CUK-H00617-63-P25691 ISSN 0006-8950

Brain

A JOURNAL OF NEUROLOGY

VOLUME 108 · PART I · MARCH 1985

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THE OCULOMOTOR BEHAVIOUR OF HUMAN ALBINOS

by H. COLLEWIJN,[1] P. APKARIAN[2] *and* H. SPEKREIJSE[2]

(From the [1]Department of Physiology I, Faculty of Medicine, Erasmus University, Rotterdam and [2]Netherlands Ophthalmic Research Institute, The Netherlands)

SUMMARY

Horizontal and vertical eye movements were recorded in 16 human albinos with a scleral search coil technique. Spontaneous nystagmus, responses to target steps, voluntary pursuit and optokinetic nystagmus (OKN) were assessed, including the effects of selective stimulation of the nasal or temporal halves of the retina. The results suggest a subdivision of albinos into three classes of oculomotor behaviour. Class I (n = 11) is characterized by vigorous spontaneous nystagmus (of the pendular unidirectional jerk or bidirectional jerk type), the absence of true horizontal OKN but the presence of the ability to control the direction of gaze in an imprecise way. In Class II (n = 2) there is a vigorous unidirectional jerk nystagmus which reverses in direction spontaneously or as a result of visual stimulation. Moving stimuli typically elicited inverted pursuit, the smooth eye movements having a direction opposite to that of the stimulus movement. Class III (n = 3) is characterized by very little or no spontaneous nystagmus and virtually normal oculomotor responses. Only pursuit of motion in the temporal direction, projected onto the temporal half retina, was defective. In all three classes, vertical eye movements were disturbed much less than horizontal. Anomalous visual projections (confirmed in all subjects by asymmetrical monocular visual evoked cortical potentials) are a likely basic cause underlying the oculomotor instability, but the large intersubject differences show that the eventual consequences of misrouting and secondary adaptations can vary widely among subjects.

INTRODUCTION

The normal histogenesis of the retina and optic tract, both derivatives of the neural ectoderm (Mann, 1949), is severely disrupted by the genetic mutation that gives rise to albinism. Functional and anatomical studies of several forms of human albinism have shown that the albino mutation affects not only the pigmented layer of the retina but also the complex neural layer (for reviews *see* Duke-Elder, 1964; O'Donnell and Green, 1979; Taylor, 1978). Corresponding anomalies of the pigment epithelium include fundus hypopigmentation (Fitzpatrick and Quevedo, 1972; Klein and Nordlund, 1981). Neural anomalies include foveal hypoplasia (O'Donnell *et al.*, 1976; Fulton *et al.*, 1978) and aberrant optic pathway projections (Guillery *et al.*, 1975). The latter take the form of a reduction in ipsilaterally destined retinofugal projections. In albinism, temporal retinal ganglion fibres which should

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project ipsilaterally instead decussate erroneously at the optic chiasma and subsequently misroute to contralateral visual projection targets, namely the lateral geniculate body and visual cortex. Comparable anomalous retinofugal projections have been demonstrated in all species of albino mammals so far investigated (*see* Witkop *et al.*, 1982).

The visual system anomalies in albinism result in two major visual complaints: reduced visual acuity and nystagmus. Acuity values in albinism typically range from 0.67 (20/30) to 0.05 (20/400) (Fonda, 1962). Reduced acuity in albinos is primarily attributed to abnormalities of the neural retina (Duke-Elder, 1964; Taylor, 1978), although other contributing factors such as high refractive error (Fonda *et al.*, 1971), interocular light scatter (Krill, 1977) and nystagmus (Loshin and Browning, 1983), are also implicated. Although the severity of visual loss has been positively correlated with several of these features, the precise causal relationship between the inherent ocular anomalies in albinism and the concomitant visual dysfunction is not yet fully understood. This is particularly true for the aetiology and functional consequences of nystagmus.

That oculomotor instability in albinism may be a consequence of aberrant retinofugal projections, signalling erroneous information concerning visual motion to intended oculomotor sites, has been considered in a series of investigations in the albino mouse (Mangini *et al.*, 1982), rat (Precht and Cazin, 1979), rabbit (Hahnenberger, 1977; Collewijn *et al.*, 1978) and man (Wildberger and Meyer, 1978). One of the common oculomotor features of these studies was a functional deficit of optokinetic nystagmus (OKN). In the study on oculomotor function in albino rabbits by Collewijn *et al.* (1978), stable eye position and relatively normal OKN were recorded with full-field stimulation. When the field was restricted to an anterior sector, eye position became unstable and optokinetic eye movements were inverted, that is, the direction of the slow eye movement was opposite to the direction of stimulus motion.

The present study is an attempt first, to describe spontaneous and elicited oculomotor behaviour systematically in a representative sample of human albinos, and secondly, to test whether the findings of inverted optokinetic responses in a part of the visual field in the rabbit can be confirmed in the human albino. A preliminary report of part of the findings has appeared (Apkarian *et al.*, 1983*b*).

MATERIALS AND METHODS

Patients

The 16 clinically diagnosed albinos who participated in this study, after informed consent, were volunteers preselected from a larger albino subject pool (> 100), all of whom had previously undergone detailed opthalmological and electrophysiological assessment. Ophthalmological examination, which included pedigree analysis, hairbulb incubation, tyrosinase assay and skin biopsy to aid in the albino typing, was performed at The Netherlands Ophthalmic Research Institute by W. Delleman and D. van Dorp.

The single most reliable pathognomonic sign of human albinism is the presence of contralateral visual evoked potential (VEP) asymmetry following monocular full-field stimulation of an appearing/ disappearing checkerboard pattern (*for details see* Apkarian *et al.*, 1983). The VEP asymmetry specific to albinism is a reflection of the underlying misrouted optic pathway projections. VEP albino screening to confirm the clinical diagnosis objectively was performed in all patients with the exception of Case 14 in whom VEP recordings were not possible because of a previous skull fracture in the region of the occiput.

A summary of the clinical histories is presented in Table 1, along with the results of the VEP and oculomotor examinations. The presence or absence of nystagmus was based both on the clinical observations as well as the results of electromagnetic recordings. In Case 16 spontaneous nystagmus, which was not detectable clinically, was apparent with high gain recordings. Following eye movement recording, albinos were grouped into one of three oculomotor categories. Although albino type is suggested (*see* Table 1), it is important to note that Van Dorp *et al.* (1982) reported that the genotype is frequently difficult to determine because phenotype, biochemical analysis (hairbulb test, tyrosinase assay) and skin biopsy are not always concordant.

TABLE 1 CLINICAL DATA FOR THE 16 ALBINO SUBJECTS

					Ophthalmological findings					
Case no	*Age (yrs) sex*	*Clinical diagnosis*	*VEP asymmetry*	*Oculomotor category (class)*	*Visual acuity*	*Fundus pigment*	*Foveal reflex*	*Iris translucence*	*Photo-phobia*	*Nystagmus*
1	20/M	TNOCA	●	I	0 1, 0 1	○	○	●	●	●
2	41/M	TNOCA	●	I	0 1, 0 16	○	○	●	●	●
3	16/M	TNOCA	●	I	0 25, 0 2	○	○	●	●	●
4	36/M	TPOCA	●	I	0 16, 0 2	○	○	●	●	●
5	22/F	TPOCA	●	I	0 2, 0 2	●	○	●	●	●
6	31/M	TPOCA	●	I	0 3, 0 3	●	○	●	⊖	●
7	34/F	TPOCA	●	I	0 4, 0 25	○	○	●	●	●
8	31/M	TPOCA AROA	●	I	0 2, 0 25	●	○	●	○	●
9	23/M	TPOCA AROA	●	I	0 25, 0 26	⊖	○	●	⊖	●
10	11/M	XOA	●	I	0 16, 0 16	●	○	●	⊖	●
11	19/M	XOA	●	I	0 2, 0 3	●	○	●	⊖	●
12	32/M	TPOCA AROA	●	II	0 2, 0 3	●	○	●	●	●
13	27/M	XOA	●	II	0 1, 0 13	●	○	●	⊖	●
14	27/M	TPOCA	●	III	0 33, 0 33	●	○	●	●	○
15	20/F	TPOCA	●	III	0 5, 0 5	●	⊖	●	●	⊙
16	21/M	XOA	●	III	0 5, 0 5	●	○	●	●	⊙

TNOCA = tyrosinase negative oculocutaneous albino TPOCA = tyrosinase positive oculocutaneous albino AROA = autosomal recessive ocular albino XOA = X-linked ocular albino ● = present. ⊖ = possibly present ○ = not detectable ⊙ = clinically not detectable ● = unable to test

Stimulation

Visual stimulation was presented under two conditions; during the course of the study most subjects, in repeated sessions, were tested with both. In one condition, various stimulus configurations (laser generated spots, film generated edges, bars, gratings and random dot backgrounds) were back-projected *via* two servocontrolled mirrors onto a translucent tangent screen placed at a distance of 1.43 m and subtending a visual angle of 90 × 90 deg. Stimulus position was controlled by a PDP 11/10 computer connected through D/A converters to the mirror galvanometers. In the second condition, a fixation spot, edges, bars or gratings were projected overhead onto a hemicylindrical screen at a distance of 0.80 m. The extent of the stimulus was 90 deg left, 90 deg right (total field 180 deg horizontally), 38 deg upwards and 67 deg downwards. Stimulus templates placed around a motor driven cylinder were projected by a central lamp. As in the prevous condition, the retinal extent of the stimulus could be adjusted by servocontrolled masks surrounding the template and driven by the eye movement signal. This allowed stimulation of selected retinal regions even in patients with nystagmus.

For calibration measures and saccadic tracking, the laser spot which subtended 7 min of arc jumped left, right, up or down in 10 deg and 20 deg steps; horizonal and vertical excursions were presented separately or in combination. To test pursuit eye movements, the laser moved in a triangular fashion left and right/up and down. For two-dimensional pursuit, the laser beam followed a rhomboid trajectory. To test OKN, square wave gratings (period 5 deg) were presented at various constant velocities from 6 to 60 deg/s, drifting either up and down or left and right. For more detailed descriptions of the stimulus conditions *see* DuBois and Collewijn (1979), Van Die and Collewijn (1982), Tamminga (1983) and Collewijn and Tamminga (1984).

Recording

Binocular or monocular horizontal and vertical eye positions were measured by electromagnetic techniques described in full detail by Robinson (1963) and Collewijn (1977). The basic technique consists of phase or amplitude detection of a signal induced in a scleral search coil by homogeneous A.C. magnetic fields. The induction coil is embedded in a silicone contact annulus which adheres comfortably and firmly to the limbic area, concentric with the cornea (Collewijn *et al.*, 1975). The dynamic range of the recording system is better than 100 Hz with a noise level of less than 3 min of arc. Recording resolution of horizontal and vertical eye position is at last 1 min of arc (*see* Tamminga, 1983). During all sessions, stimulus profile, eye position and eye velocity were written on a pen recorder, recorded on magnetic tape and stored on disc.

Procedure

To minimize head movement, subjects were seated with head supports and a chin rest. Since a calibration procedure dependent on the fixation of a target displaced in steps, as is customary with normal subjects, could not be relied upon in albinos with unsteady eyes, the gains of all annuli were precalibrated by rotation through fixed angles in a calibration device. The absence of cross-talk between horizontal and vertical channels was checked and if necessary achieved by appropriate adjustment of the phase references of the lock-in amplifiers. As the position of the coil on the eye varies between subjects, the zero settings had to be adjusted while subjects attempted to fixate a stationary target in the centre of the screen. Recording one eye was standard but occasionally movements of both eyes were recorded. Binocular as well as monocular viewing was employed. Recordings were performed in complete darkness or with dim room-light illumination depending on the experimental series. For OKN recordings, subjects were instructed to attend to the moving stripes without attempting to pursue a single stripe. Each session lasted about 30 min and consisted of about 20 different test conditions; these will be described in the Results section.

RESULTS

On the basis of the spontaneous nystagmus and the responses to moving visual targets it was possible to divide our sample of albinos into three classes. The typical oculomotor profile for each class will be described in terms of the pattern of the spontaneous nystagmus, the response to steps and continuous displacement of the target, and the optokinetic responses. Several other paradigms were tested including open-loop conditions, achieved by a 1:1 feedback of the eye position to the target position. Under this condition fixed position errors or slip velocities of the target could be imposed on the retina. As the results of these unusual stimulation conditions were inconsistent and inconclusive they will not be described.

Class I

Class I (11 subjects, *see* Table 1) is characterized by the presence of vigorous spontaneous nystagmus and the absence of a true OKN in the horizontal plane, with retention of the ability to direct the gaze in an imprecise fashion to distinct stationary or moving targets. In contrast, vertical eye movements show relatively little abnormality.

Spontaneous nystagmus. The observed waveforms of the horizontal nystagmus are comparable to the various types of congenital nystagmus described systematically by Dell'Osso and Daroff (1975). All types of congenital nystagmus reported in their classification scheme were recorded in the present study in certain subjects at certain times. In most subjects of Class I, nystagmus was dominated by one or two basic waveforms (Table 2) but other types appeared transiently or under specific conditions. The most common forms of nystagmus were, in order of prevalence: pseudocycloid, pendular, pseudopendular and pseudojerk. Typical peak-to-peak

TABLE 2. SUMMARY OF THE PROPERTIES OF SPONTANEOUS NYSTAGMUS IN THE 16 ALBINO SUBJECTS

Case no.	*Dominant waveform*	*Amplitude (deg)*	*Maximal velocity (deg/s)*
1	Asymmetric pendular (with braking saccades)/pseudojerk	5–10	25–80
2	Pseudocycloid/pendular	5	80
3	Pseudocycloid/pendular	10–20	110
4	Pseudopendular	5–10	75
5	Pseudocycloid	5–10	100
6	Pseudojerk/pendular (with braking saccades)	5	10–50
7	Pseudocycloid	3	50
8	Pseudopendular/pseudocycloid	5	50
9	Pseudocycloid/pseudopendular	1–5	30
10	Pseudojerk/pendular	2–5	50
11	Dual jerk	2	5
12	Pseudocycloid	5	25
13	Pseudocycloid	5	50
14	Almost normal fixation	1	0.5
15	Almost normal fixation	0.5	0.5
16	Pure jerk	1	2

amplitudes were about 5 deg, with nonsaccadic velocities often reaching 50 to 100 deg/s. The basic pattern of nystagmus for Class I albinos is shown (figs. 1–2) for 2 subjects with visual acuities ranging from 0.1 (20/200) to 0.25 (20/80), as listed in Table 1. The spontaneous nystagmus is presented under four standard conditions: (1) binocular fixation of a point target which was displaced in steps of 10 deg around the centre every 3 s (column 1); (2) darkness (column 2); (3) right eye fixation of a stationary point target (left eye occluded; column 3); and (4) left eye fixation of a stationary point target, right eye occluded (column 4).

Case 1 (fig. 1) showed a coarse horizontal nystagmus of a rather bizarre shape varying between asymmetric pendular with occasional braking saccades and a pseudojerk pattern. (The term 'foveating saccades' is avoided in view of the maldevelopment of the fovea in albinos.) Periods of zero velocity were infrequent. Vertically the eye was relatively stable, although the nystagmus clearly had a small vertical component (amplitude 1–2 deg; velocities up to 15 deg/s). The vertical nystagmus is not due to cross-talk in the recording apparatus, since in our system cross-talk (due to inappropriate phase setting) shows up as an exact, scaled down replica of the horizontal in the vertical signal and *vice versa*. Darkness did not induce

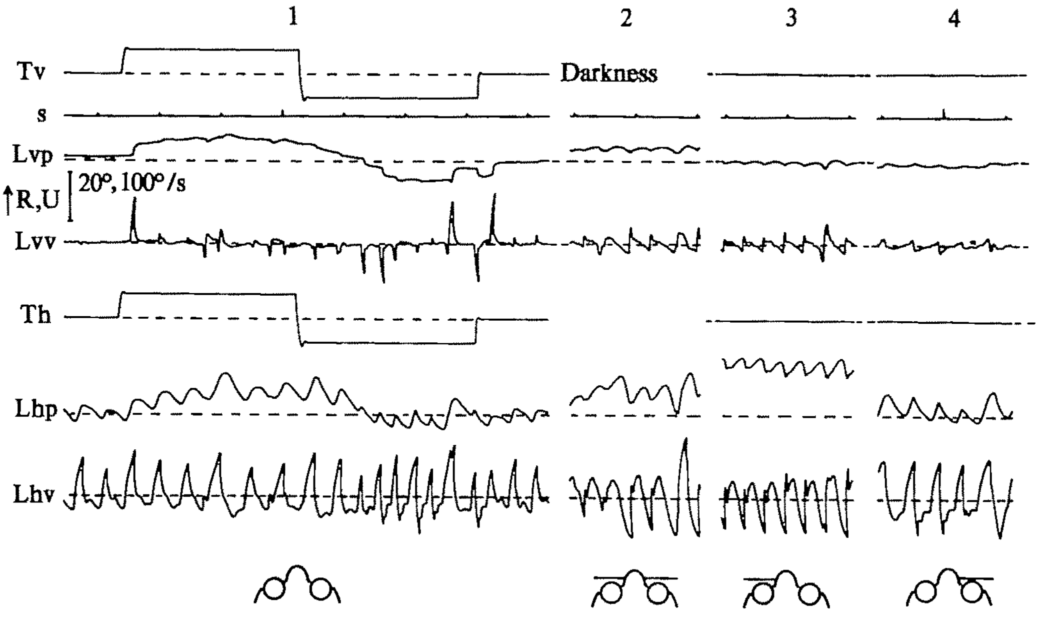

FIG. 1. Class I albino nystagmus, primarily of asymmetric pendular type with braking saccades (columns 1, 2, and 3), and secondarily, pseudojerk (columns 1 and 4), from Case 1 with low visual acuity (0.1, 0.1) L indicates left eye recording, time scale (in s) in second line. Vertical eye position (vp), corresponding vertical velocity (vv), horizontal eye position (hp) and corresponding horizontal velocity (hv) are depicted for: (1) point target (T) displacements of 10 deg, vertical (Tv) and horizontal (Th) about every 3 s, both eyes fixating (column 1); (2) during darkness (column 2); (3) stationary point target, right eye fixating (column 3); and (4) stationary point target, left eye fixating (column 4). Dashed lines indicate zero levels. Right (R) or upward (U) eye movement is represented by an upward pen deflection (curvilinear).

any significant change in either the amplitude or velocity of the nystagmus. Monocular fixation of the point target had several effects. First, when the recorded (left) eye was seeing, it was directed in such a way that one extreme of the oscillations (corresponding to velocity minima) was aligned with the target, in agreement with the descriptions by Dell'Osso (1973) and Dell'Osso and Daroff (1975). When the nonrecorded (right) eye was viewing, the nonseeing (left) eye showed considerable esophoria (angle in recording 22 deg but variable). Finally, the preferential direction of the nystagmus inverted with alternating occlusion (change in eye position may also be a contributing factor) such that the saccadic components were predominantly directed towards the seeing eye. This was a general property found in most of our subjects. It is also possible that these directional responses could be interpreted as a 'latent' component of the nystagmus, but this is unlikely as binocular viewing did not reduce the intensity of the nystagmus.

A second subject, Case 8 (fig. 2), showed horizontal jerk nystagmus either bidirectional pseudopendular, or unidirectional pseudocycloid. The overall amplitude of the nystagmus was about 5 deg; nonsaccadic velocities reached about 50 deg/s but the velocity trace showed near-zero minima, once or twice per second. The vertical component of the nystagmus was small. In darkness the spontaneous

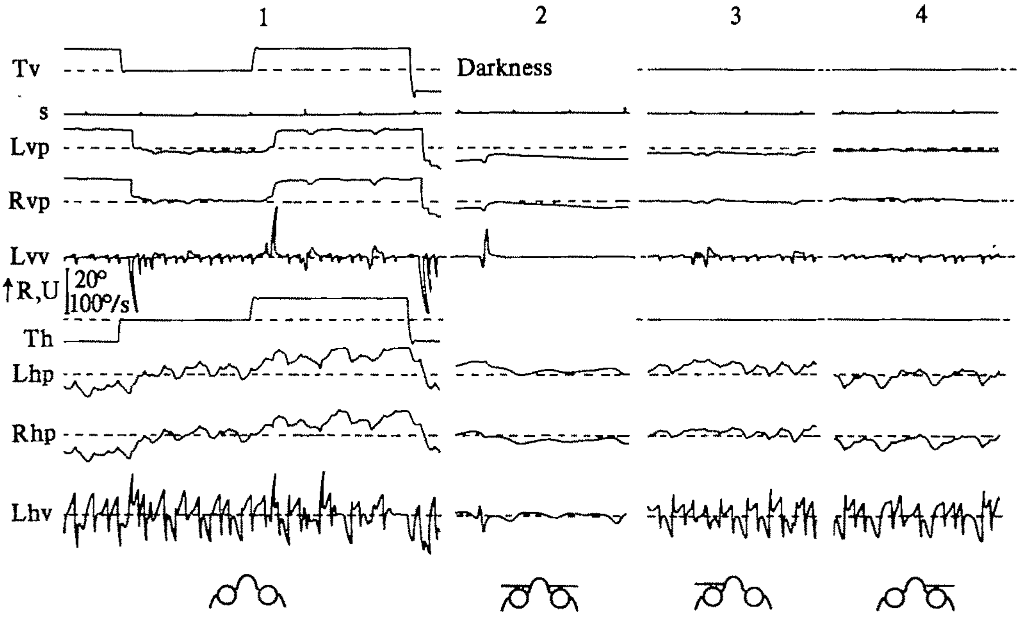

FIG 2. Class I albino nystagmus of bidirectional pseudopendular type (columns 1, 3 and 4) with episodes of unidirectional pseudocycloid nystagmus, e.g. beats 3, 4 and 5, left or right eye horizontal position, hp, column 1 for Case 8 with higher visual acuity (0.2, 0.25) than Class I subject of fig. 1. Right eye vertical position (Rvp) and right eye horizontal position (Rhp) are also depicted; all other symbols and conditions are the same as in fig. 1. The zero velocity segment of trace Lhv (column 1) occurring after 6 s is due to saturation of the position trace.

nystagmus was much diminished. This, however, was an unusual property, found only in one other subject (Case 9, not illustrated), who showed a similar pattern of pseudocycloid/pseudopendular nystagmus in the light. Monocular viewing did not change the type of nystagmus nor did it bias the pseudopendular/pseudocycloid beats clearly into one direction or reveal a phoria. Both eyes were recorded in this subject as seen from the left and right eye position traces; as the movements were conjugate under all conditions, velocity traces are presented for left eye responses only.

Response to steps of target. All subjects showed some ability to redirect the gaze approximately when the target was displaced in steps. The precision of this tracking varied considerably. Case 1 followed horizontal steps only with a slow and imprecise shift of the average gaze position without a recognizable saccadic response. Vertical steps were followed by a very slow motion consisting of a mixture of saccades and smooth movements, even though the target steps were much larger than the amplitude of the nystagmus in the vertical direction. This is illustrated in fig. 1 for combined horizontal and vertical steps, which induced similar response profiles. The abnormal vertical response to target steps was not due to an inherent oculomotor defect, as at other moments this subject showed large spontaneous

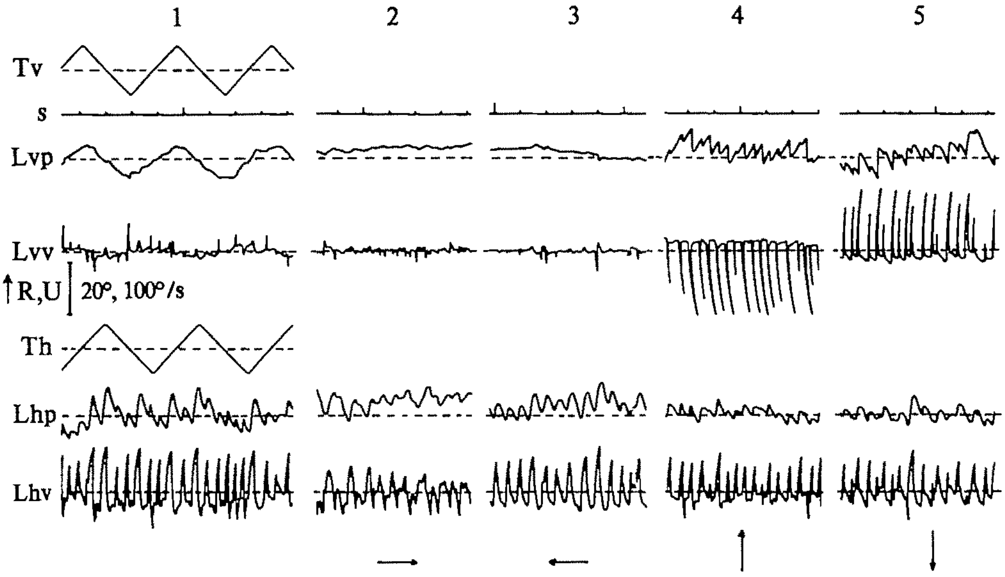

FIG. 3. Pursuit and OKN in Class I subject, Case 1 (*see* fig. 1). Pursuit was induced by a point target (T) in rhomboid trajectory (column 1). Vertical pursuit is relatively good while rudimentary horizontal pursuit superimposed on the autonomous nystagmus is difficult to detect. Remaining recordings depict OKN induced by a grating drifting at 47.6 deg/s to the right (column 2), left (column 3), up (column 4) and down (column 5) as indicated by the direction of arrow. Although horizontal OKN is absent (Lhp and Lhv, columns 2 and 3), vertical OKN shows a gain of about 0.37 in an upward direction and about 0.33 downward. Eye position was recorded during binocular viewing with the left eye bearing the coil.

vertical saccades of normal velocity. Case 8 (fig. 2) shifted his average ocular position more promptly after horizontal target steps but a distinct saccadic response was absent as well. In contrast, Case 8 responded to vertical target steps with saccades which were appropriate in size and timing. It can be stated that in general the precision of fixation and the response to steps was positively correlated with the clinically determined visual acuity. It is of interest to note that horizontal nystagmus was not affected by horizontal eye position in the range tested (10 deg up or down).

Pursuit of continuous target motion. Subjects responded to continuous motion of the target (11 deg/s, rhomboid trajectory) with an imprecise, more or less continuous displacement of the average horizontal eye position without any overt change in the pattern of nystagmus. The precision varied in a similar way as the responses to steps of target displacement. Accordingly, Case 1 (fig. 3, column 1) showed only a rudimentary horizontal response, whereas a triangular modulation of eye position was clearly present for Case 8 (fig. 4, column 1). These responses cannot be considered as genuine smooth pursuit. The target velocities were much slower than the ongoing nystagmus velocities; target velocities in excess of these would be beyond the smooth pursuit range even in normal subjects. In many instances the

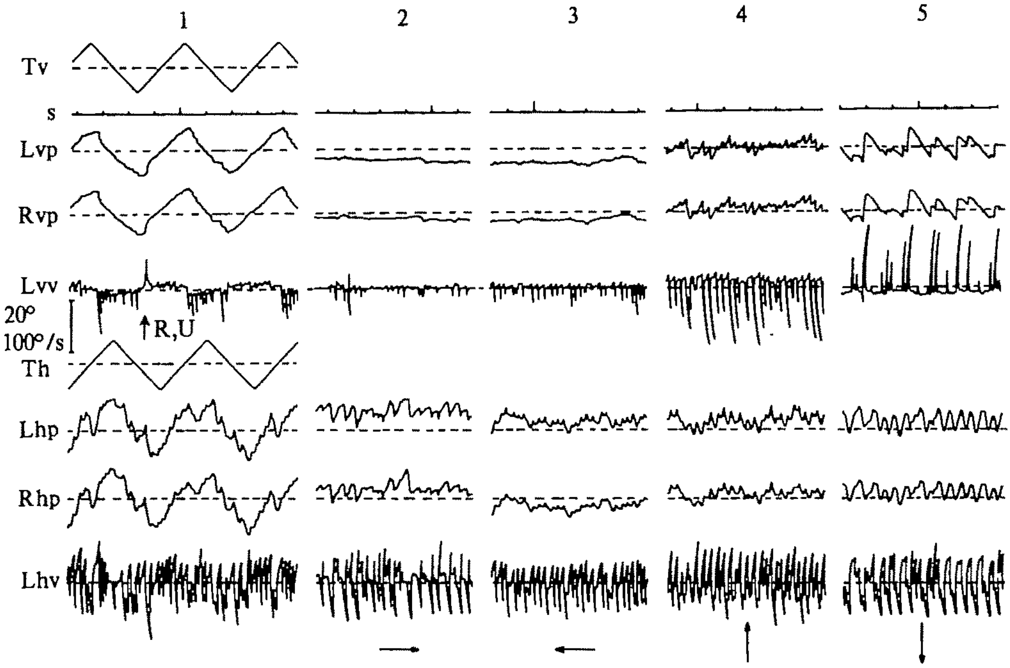

FIG. 4. Pursuit of point target (column 1) and OKN (remaining columns) in Class I subject, Case 8 (*see* fig. 2). Recordings from both eyes simultaneously; velocities only for left eye. Conditions as in fig. 3. Vertical pursuit is relatively good, while horizontal pursuit is poor but shows triangular modulation of eye position (column 1). Horizontal OKN is virtually absent (columns 2 and 3). Vertical OKN is clearly present with a gain of about 0.32 in the upward direction (column 4) and about 0.21 downwards (column 5).

smooth eye movements ran opposite to the average 'pursuit' motion, which was in such cases mainly saccadic. In Case 8 (fig. 4) both the saccadic and smooth components were modulated in magnitude to achieve imprecise tracking but no true modulation of the pseudocycloid beat direction in phase with the pursuit direction could be identified. In all cases, vertical smooth pursuit was truly present to some degree (figs. 3 and 4), as shown by the rectangular component in the vertical velocity traces.

Optokinetic stimulation. Organized OKN responses to large field (90 × 90 deg) drifting gratings moving horizontally at velocities from 6 to 60 deg/s were virtually absent in most Class I subjects. Figs. 3 and 4 show Class I responses to a grating drifting at 47.6 deg/s rightward (column 2), leftward (column 3), upward (column 4) or downward (column 5). Horizontal OKN was defective with binocular as well as monocular viewing, and also when only one half of the retina (or a slightly larger or smaller retinal sector) was selectively exposed to the moving patterns. In no Class I case could the retina be divided into parts with normal and abnormal (e.g. inverted) OKN responses; the spontaneous nystagmus continued to follow its autonomous pattern and was unaffected by optokinetic stimuli in any part of the visual field.

An apparent exception to the absence of horizontal OKN was recorded in 3 subjects (Cases 7, 10 and 11) during voluntary pursuit of a single stripe over a large excursion. An example of this behaviour is shown (fig. 5) for Case 11 who had a dual nystagmus (jerk with fine pendular components) during binocular (column 1, upper traces), right eye (column 2, lower traces) or left eye (column 5, lower traces) fixation of a stationary point target and a pure pendular nystagmus in the dark (column 1, lower traces). During pursuit the pendular components were often biased in the pursuit direction, but much of the pursuit was effected by saccades. At low stimulus velocities (6 deg/s) Case 11 followed a single stripe of the grating over a very large visual angle, subtending about 75 deg (fig. 5, columns 4 and 5, upper traces), indicating that the direction of drift and saccades was mainly determined by the position of the eye in the orbit. In the midposition (with binocular viewing) the nystagmus was symmetric pendular with few saccades; in eccentric positions a drift towards the primary position developed on top of the pendular oscillation. This drift was corrected by saccades to maintain eccentricity. While the gaze moved slowly across the midline during pursuit the direction of the nystagmus changed but the directions of drift and saccades were unrelated to the rightward or leftward direction of the stimulus motion. The nystagmus was not only affected by eye position, but also by interaction between the eyes; monocular viewing introduced a drift in the nasal direction with saccades in the direction (temporal) of the viewing eye (fig. 5, columns 2–7, lower traces), possibly due to a 'latent' component in the nystagmus. These results are in accord with previous descriptions (Dell'Osso *et al.*, 1974). Monocular pursuit was much smoother in the nasal than in the temporal direction.

In sharp distinction to the absence of true horizontal OKN, vertical OKN was easily elicited in all subjects tested. Even in subjects with otherwise very poor

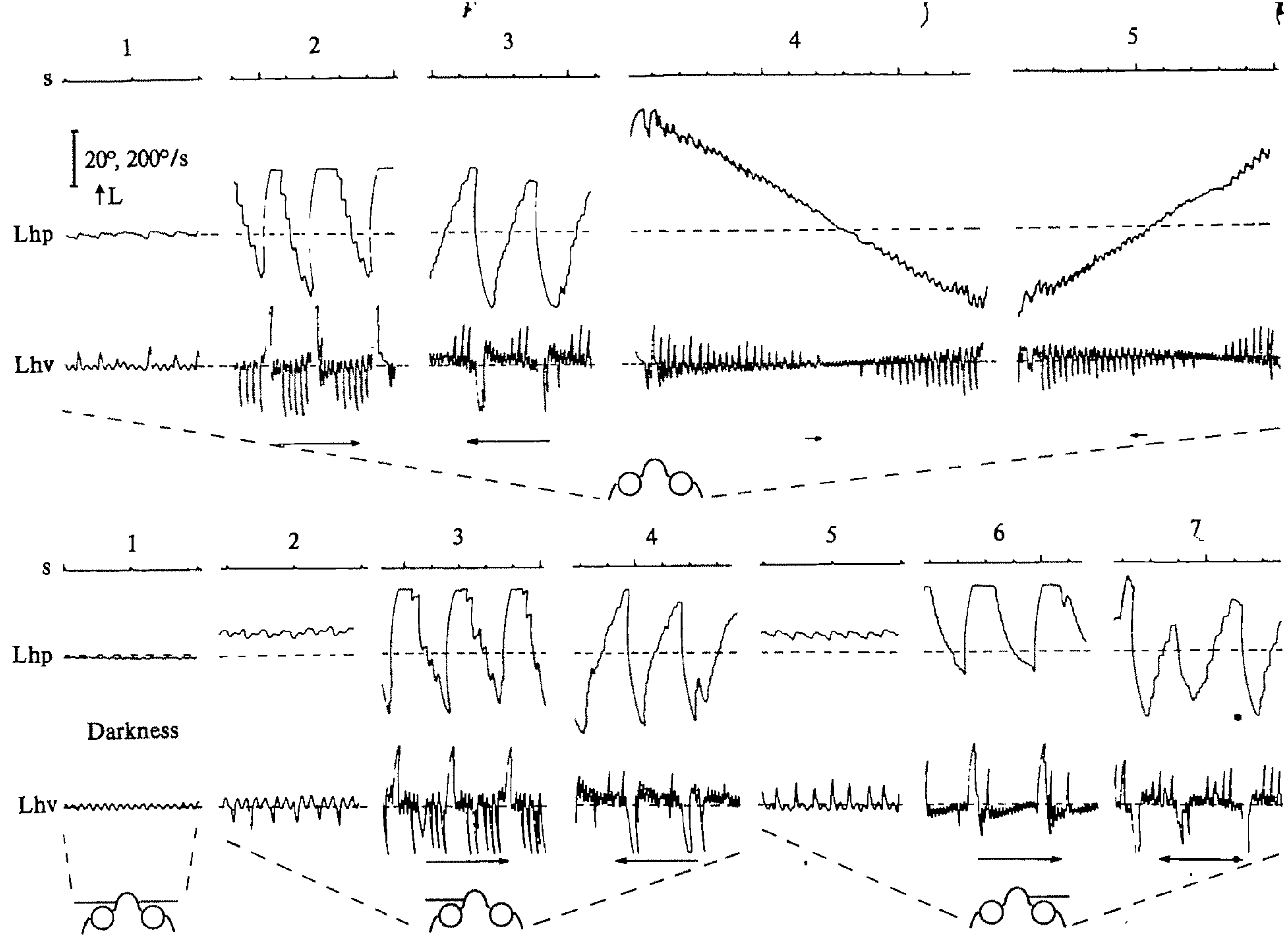

FIG. 5. Oculomotor responses for Class I subject, Case 11. Note that in contrast to all other figs. in this illustration, rightward (R) eye movement is represented by a downward pen deflection, leftward (L) by an upward deflection. Only horizontal (h) position (p) and velocity (v) are shown. Upper three rows depict binocular fixation to a stationary point target (column 1) and OKN with binocular viewing of a grating drifting at 30 deg/s rightward (column 2) or leftward (column 3) and at 6 deg/s rightward (column 4) or leftward (column 5). Lower three rows depict nystagmus during darkness (column 1), right eye viewing of a stationary point target (column 2) or grating drifting at 30 deg/s rightward (column 3) or leftward (column 4) and left eye viewing under the same conditions (last three columns).

oculomotor responses such as Cases 1 (fig. 3) and 8 (fig. 4), vertical OKN (columns 4 and 5) was well developed and consisted of a regular sequence of fast and slow phases with a moderate amplitude. The gain of the slow phase velocity (fraction of stimulus velocity), however, was low (0.21–0.42) in all subjects tested in this class. Vertical optokinetic pursuit did not appear systematically to affect horizontal nystagmus.

Class II

Class II (2 subjects, Cases 12 and 13) is characterized by the presence of a vigorous unidirectional jerk nystagmus which reverses in direction. Responses to moving stimuli were inverted in the sense that the fast phase was directed in the pursuit direction and the smooth phase was in the opposite direction. This inversion was present in the responses to discrete targets (small spots, single bars) as well as large field gratings.

Spontaneous nystagmus. The spontaneous nystagmus in subjects of Class II was of the jerk type, frequently pseudocycloid and occasionally pure jerk. The direction was variable. First, with binocular viewing spontaneous reversals occurred at irregular and unpredictable intervals. Fig. 6B and C illustrate a typical spontaneous reversal during binocular viewing for Case 13. During the period of changing direction the pseudocycloid pattern changed into a transient triangular nystagmus lasting about 10 s, after which the pseudocycloid pattern resumed in reversed direction. Before and after the reversal the low velocity segments of the pseudocycloid beats were more or less aligned with the target. With monocular viewing, there was a rather strong tendency for the nystagmus to beat in one preferred direction (fig. 7). In Case 13, the direction of preference followed the general rule of fast phases beating in the direction of the seeing eye. When the nystagmus had been beating for some time to the left with the right eye covered (left eye viewing), changing the occlusion to the left eye would often induce a reversal (fig. 7A). It should be noted, however, that such reversals were not obligate, nor could they be induced repeatedly within short intervals. In Case 13, the reversal was not accompanied by a large shift in eye position, except that the nystagmus beat either to the left or to the right of the visual target; recordings from this subject did not indicate a significant phoria. In Case 12 (fig. 7B) the directional preference was against the rule; that is, with monocular viewing the fast beats usually (but not obligately) beat towards the covered eye. The low velocity segments of the nystagmus of the viewing eye were approximately aligned with the target (figs. 7B and 8, columns 3 and 4) as far as could be determined from the voluntary fixation epochs; recordings from Case 12 showed an exophoria of about 13 deg (not constant). As the predominant instabilities were opposite for viewing with the left and right eye stimulated separately, we looked for evidence of any cancellation of this tendency which might be manifest as a more stable binocular than monocular fixation. This effect was indeed present in Case 12 (fig. 8, columns 1, 3, 4 and 5). The consistently improved binocular stability of this case may be related to a positional effect as both eyes were well aligned with the target during binocular viewing while during monocular viewing the occluded eye was abducted. The binocular improvement cannot be interpreted as a conventional latent nystagmus since the monocular nystagmus was usually beating with the fast phase to the nasal side.

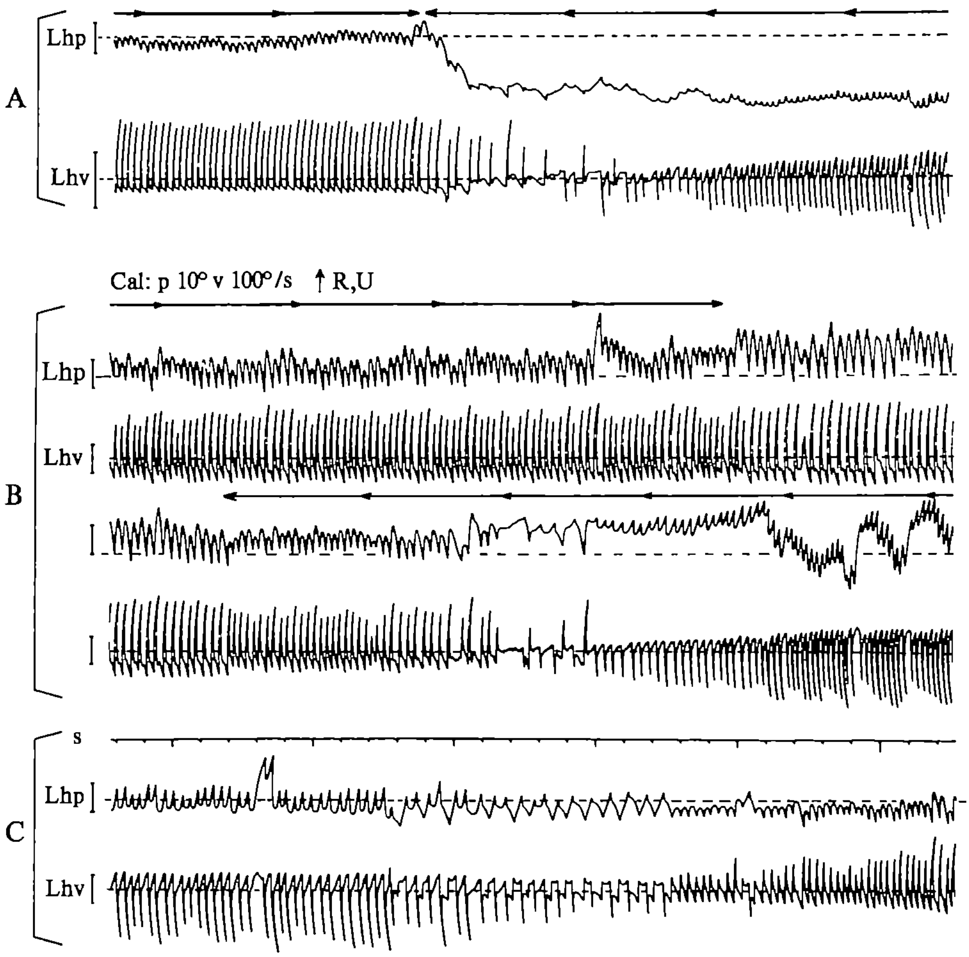

FIG. 6. Class II inverted OKN and spontaneous nystagmus reversal. A, left eye recording of OKN elicited by target motion (grating drifting at 30 deg/s to the right, *see* arrow direction) or left in Case 12 with left eye viewing. Initial nystagmus shows a fast phase to the right corresponding to the monocular direction preference of this subject (*see* fig. 8). Prompt inversion of the nystagmus follows OKN stimulation in a leftward direction. Note also that with leftward OKN, the average left eye position rotates to the left; with rightward stimulation the eye remains straight ahead. Eccentricity also induces drift toward the midposition and jerks towards the periphery. B, continuous left eye recording for target motion to the right (*see arrow*), during darkness, and to the left (*see arrow*) in Case 13 with both eyes viewing. OKN inversion is clearly present but occurs only after a delay period. Unlike Case 12, the direction of nystagmus for Case 13 is not coupled with eye position; the direction of drift towards or from the midposition is not constant. C, spontaneous inversion of nystagmus for Case 13 with both eyes viewing a stationary point target. The nystagmus takes the form of pseudocycloid left, pseudopendular and triangular (during inversion), followed by pseudocycloid right.

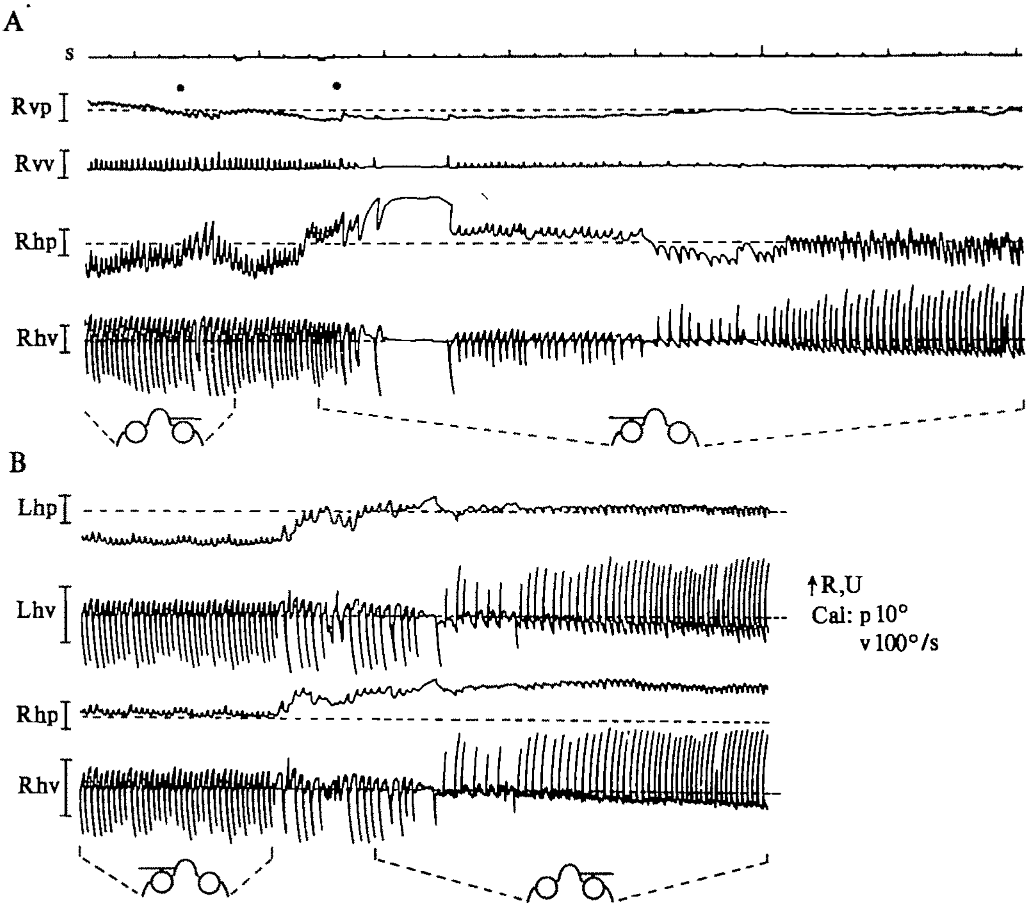

FIG. 7 Class II inverted nystagmus induced by alternating occlusion. A, inversion of nystagmus for Case 13 from left to right eye viewing. The fast phase beats in the direction of the viewing eye. Note that the nystagmus type is pseudocycloid and that nystagmus direction is not coupled to average eye position. B, inversion of nystagmus for Case 12 from right to left eye viewing. In contradiction to the rule, the jerks beat in the direction of the covered eye. Note the relation between nystagmus direction and eye position. Note also that nystagmus velocity for Case 13 about twice as high as for Case 12.

Case 13 did not show a similar improvement of stability during binocular vision. His nystagmus velocities were about twice as high as in Case 12. Darkness did not improve stability in either subject (shown for Case 12 in fig. 8, column 2). All eye movements were essentially conjugate. Both these cases showed only little spontaneous nystagmus in the vertical direction (figs. 7, 8).

Response to steps. Horizontal target steps were followed rather promptly and precisely by appropriate displacements of the average eye positions. In Case 13 the nystagmus shape was unchanged by position displacement in steps of 10 deg (not illustrated); during binocular viewing Case 12 showed a tendency to direct the slow

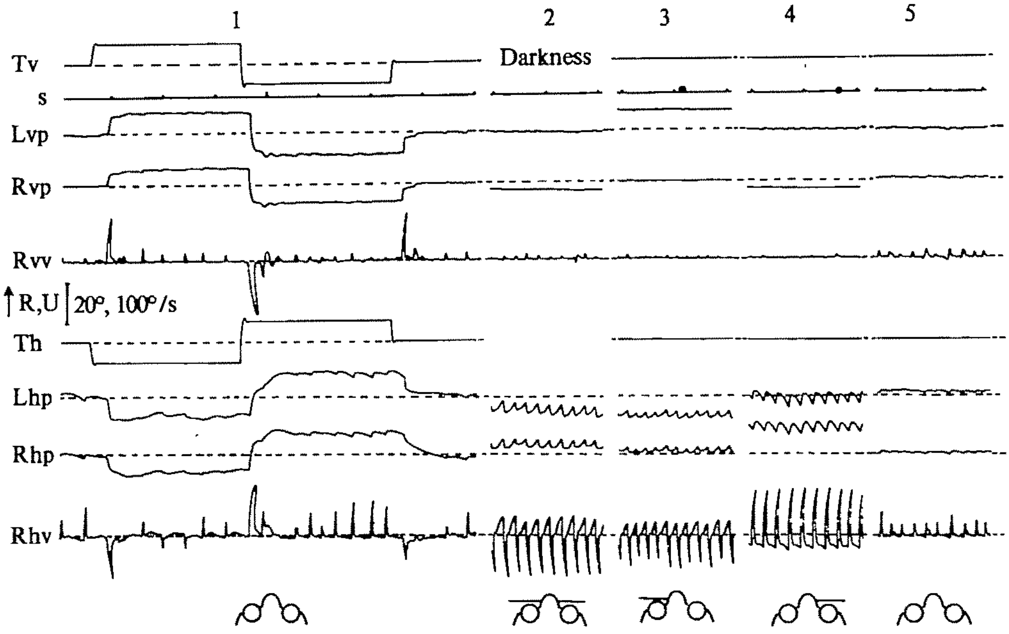

FIG. 8. Nystagmus of pseudocycloid type for Class II subject, Case 12. Recordings from both eyes simultaneously; velocities shown for right eye only. Binocular fixation of target displaced in steps (column 1), darkness (column 2), fixation of a stationary point target with right eye (column 3) and left eye only (column 4) and subsequent return to binocular fixation (column 5).

movement towards the primary position when the target and therefore eyes were positioned 10 deg right or left of centre (fig. 8, column 1).

Pursuit of continuous target motion. Voluntary pursuit was mainly achieved by saccades. Fig. 9 shows this clearly for Case 12. With binocular viewing (column 1), the saccades were predominantly in the direction of pursuit, while the smooth components were position-dependent and typically directed towards the primary position, independent of the direction of pursuit. With monocular viewing (fig. 9, columns 2 and 3), although the nystagmus continued to beat in one direction, the frequency of the saccades was modulated to track the target. Remarkably, in Case 12 monocular pursuit abolished the against-the-rule tendency to beat towards the occluded eye and induced the with-the-rule beating towards the seeing eye. In Case 13, who was less position-dependent, a strong effort to pursue resulted in bursts of saccades in the pursuit direction, while the smooth components followed the opposite direction (not illustrated).

It can be concluded that subjects of Class II showed no true horizontal smooth pursuit but rather a tendency to inversion of the smooth component. In contrast, vertical pursuit was essentially normal with smooth tracking in the direction of the target, assisted by frequent saccades in the same direction (fig. 9, upper traces).

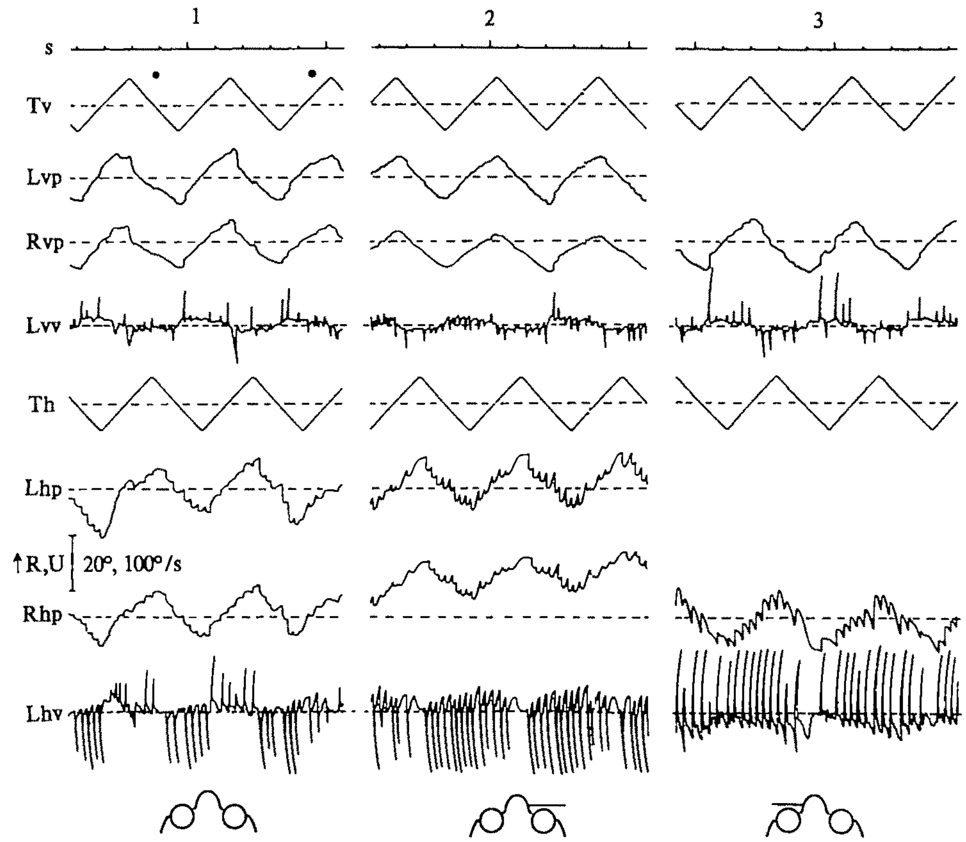

FIG. 9 Class II albino pursuit induced in Case 12 by a point target (T) in rhomboid trajectory (*see* figs. 4 and 5 for further details) for binocuolar (column 1), left eye (column 2) and right eye (column 3) viewing Binocular vertical pursuit shows appropriate velocity trajectories. Binocular horizontal pursuit shows saccadic following with the smooth phase frequently in the wrong direction, i.e. opposite to target motion. Note that rightward and leftward pursuit are relatively symmetrical Monocular vertical pursuit remains fairly good. Monocular horizontal pursuit, however, shows that imprecise pursuit occurs as a result of modulation of the frequency of jerks. With left eye viewing, the spontaneous nystagmus horizontally beats fast phase to the left (obeying the rule but atypical for this subject) With right eye viewing, the fast phase beats to the right. Recordings from both eyes, except for right eye viewing (column 3) with recording of right eye position and velocity only. Note the presence of exophoria and compare with that depicted for the same subject in fig. 8.

Optokinetic responses. Inverted OKN reactions were reliably induced in Class II subjects by large gratings moving steadily in one direction at a velocity of 30 deg/s. Lower and higher velocities produced this phenomenon less consistently. The response to an OKN stimulus consisted of a continuation of the ongoing nystagmus when the stimulus moved into the direction of fast phases, and an inversion when the stimulus was in the opposite direction (fig. 6). The inversion was rather prompt and was accompanied by a shift in position in the direction of the stimulus motion in Case 12 (fig. 6, upper traces, left eye viewing); in the eccentric position the smooth component was directed toward the primary position. This reversal was achieved with monocular viewing; optokinetic stimulation overruled the preference induced by monocular viewing in determining the nystagmus direction. In Case 13 reversed OKN was induced without an obligate shift in average gaze direction (fig. 6, middle traces, binocular viewing).

Optokinetic stimuli induced the reported inversions much more consistently and reliably than other procedures including alternating occlusion of one eye or pursuit of a small target. It should be emphasized, however, that the optokinetic response consisted only of an inversion of the ongoing nystagmus; its other parameters were unaffected and there was no relation between stimulus velocity and eye velocity. Furthermore, selective stimulation of the nasal or temporal retina, tested with the field border stabilized at a number of different locations around the fixation point, did not reveal a division of the retina into normal and abnormal parts (not illustrated). Ocular stability or normal OKN could not be obtained from either half retina.

Class III

Class III (3 subjects, *see* Table 1) is characterized by the virtual or complete absence of nystagmus and normality of oculomotor responses. Defects were detected only during pursuit of temporal motion projected onto the temporal half retina.

Spontaneous nystagmus. Clinical observation did not reveal nystagmus in any of the Class III subjects, but recordings with increased sensitivity showed a systematic pure jerk nystagmus in Case 16 (fig. 10). The nystagmus always beat with the fast phase to the left and was most pronounced during monocular viewing with the left eye (column 5). The peak-to-peak amplitude was about 1 deg and slow phase velocities did not exceed 2 deg/s. With binocular viewing the nystagmus was also present but it disappeared during monocular viewing with the right eye and also during darkness. When it was present the nystagmus was essentially conjugate and sometimes had a vertical component. Thus, nystagmus for Case 16 was apparently elicited by visual stimulation of the left eye only. In the 2 other subjects of this class (Cases 14 and 15, fig. 11) the eyes were more stable. Case 14 showed considerable drift, typically about 0.5 deg/s in both left and right directions with frequent microsaccades; Case 15 showed a consistent drift to the right and downwards at maximally 1 deg/s. Although such performances shows rather imprecise fixation it does not qualify as nystagmus.

Responses to steps. Steps of the point target were followed promptly and precisely in the horizontal as well as vertical direction. The frequent undershoot with secondary and tertiary corrective saccades present in fig. 10 for Case 16 was not typical; Cases 14 and 15 showed completely normal step responses.

Smooth pursuit. In all 3 subjects of this class, true smooth pursuit was used to track the point target moving in a rhomboid trajectory (fig. 12, Case 16). Although saccades were used in addition to smooth tracking, these accounted only for a

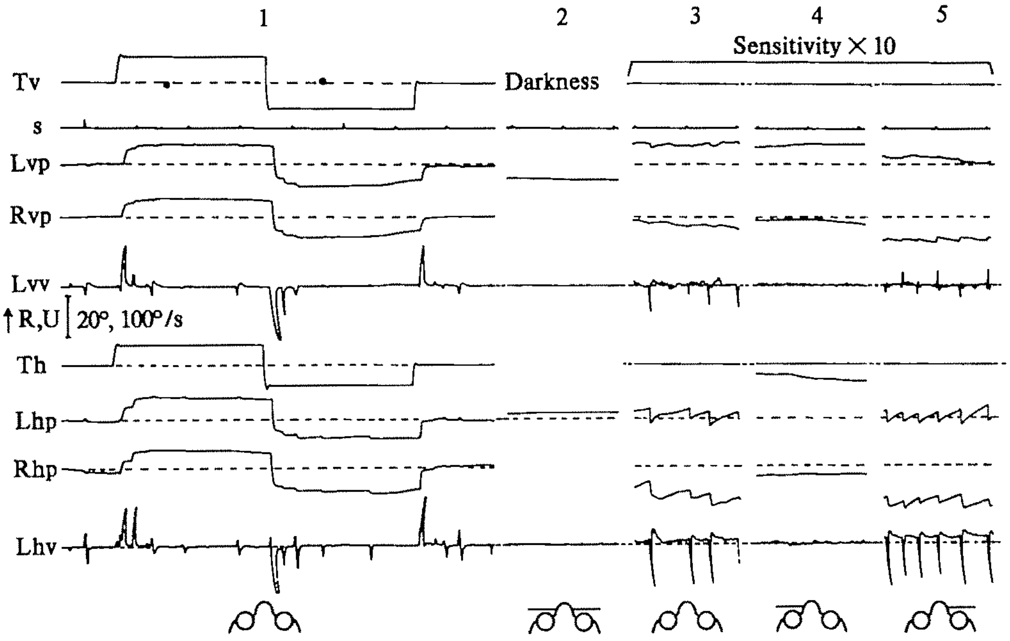

FIG. 10. Nystagmus of the pure jerk type (left beating) with small amplitude in Class III subject, Case 16. Binocular viewing of point target displacements is illustrated in column 1; during darknes in column 2. Binocular viewing of a stationary point target is illustrated in column 3; right eye viewing, column 4; left eye viewing, column 5. Note that the sensitivity for the latter three conditions was increased by a factor of 10, i.e. calibration bar now equals 2 deg, 10 deg/s.

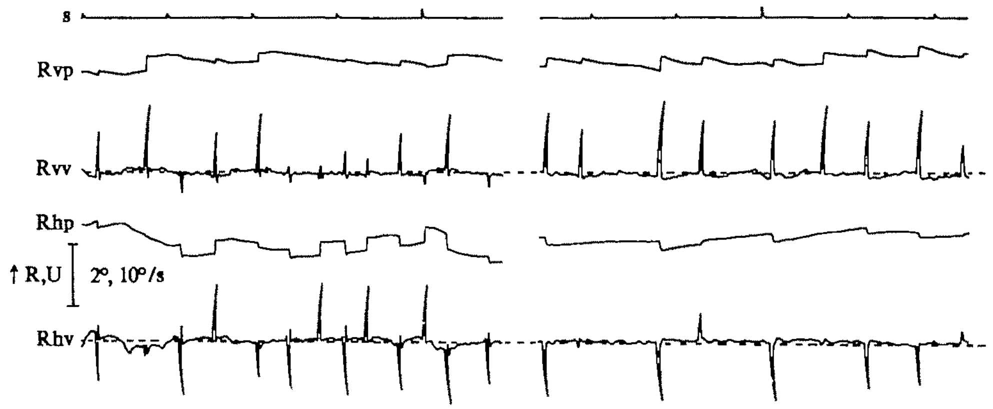

FIG. 11. Binocular fixation of a stationary point target for Class III subjects, Cases 14 (column 1) and 15 (column 2). Note the increase in sensitivity (*see* calibration scale). For both cases, the fixation instability is almost within normal limits.

small part of the pursuit. The velocity traces showed the rectangular modulation characteristic for normal pursuit of a triangular motion. The overall gain of the composite eye movements (smooth and saccadic) was about unity. This performance is comparable to that found in normals under similar conditions (Collewijn and Tamminga, 1984).

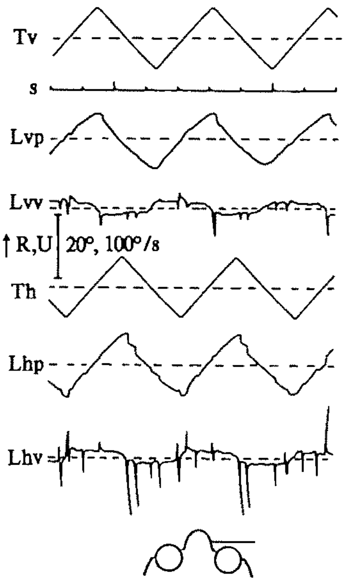

FIG. 12. Class III pursuit for Case 16 in the viewing (left) eye. For further details, *see* fig. 3. True pursuit is clearly present but is consistently less stable with rightward tracking than with leftward in accordance with the direction of spontaneous nystagmus for left eye viewing (*see* fig. 10), i.e. nasalward pursuit is smoother than temporal. Note also that most saccades are in the left and downward direction and that vertical pursuit is smoother than horizontal.

Optokinetic nystagmus. Responses to a full-field (180 deg) grating pattern moving at 30 deg/s are shown for Case 16 in fig. 13A. With binocular (columns 1-2) as well as monocular (columns 3-6) viewing of either eye, excellent tracking was elicited with a slow-phase velocity gain of 0.90 to 1.03, symmetrical in both directions. The large amplitude of the beats suggests the presence of voluntary pursuit in addition to OKN. Cases 14 (fig. 14) and 15 (not illustrated), investigated with a smaller stimulus field (90 × 90 deg), showed a regular OKN with smaller beats and gains of 0.23 to 0.47 and 0.55 to 0.59, respectively.

An anomaly of OKN was revealed in 2 of the 3 subjects of this class by half-field stimulation (fig. 13B and fig. 14, columns 3-6). With selective stimulation of the temporal retina (stripes visible in nasal visual field only) motion of the stripes in the nasal direction was followed well with a gain up to 1.0 in Case 16 (fig. 13B, column 2) and up to 0.46 in Case 14 (fig. 14, column 6). In contrast, motion in the temporal direction mainly elicited saccades towards the sector of the visual field where the stripes were visible without any systematic smooth tracking. Any smooth

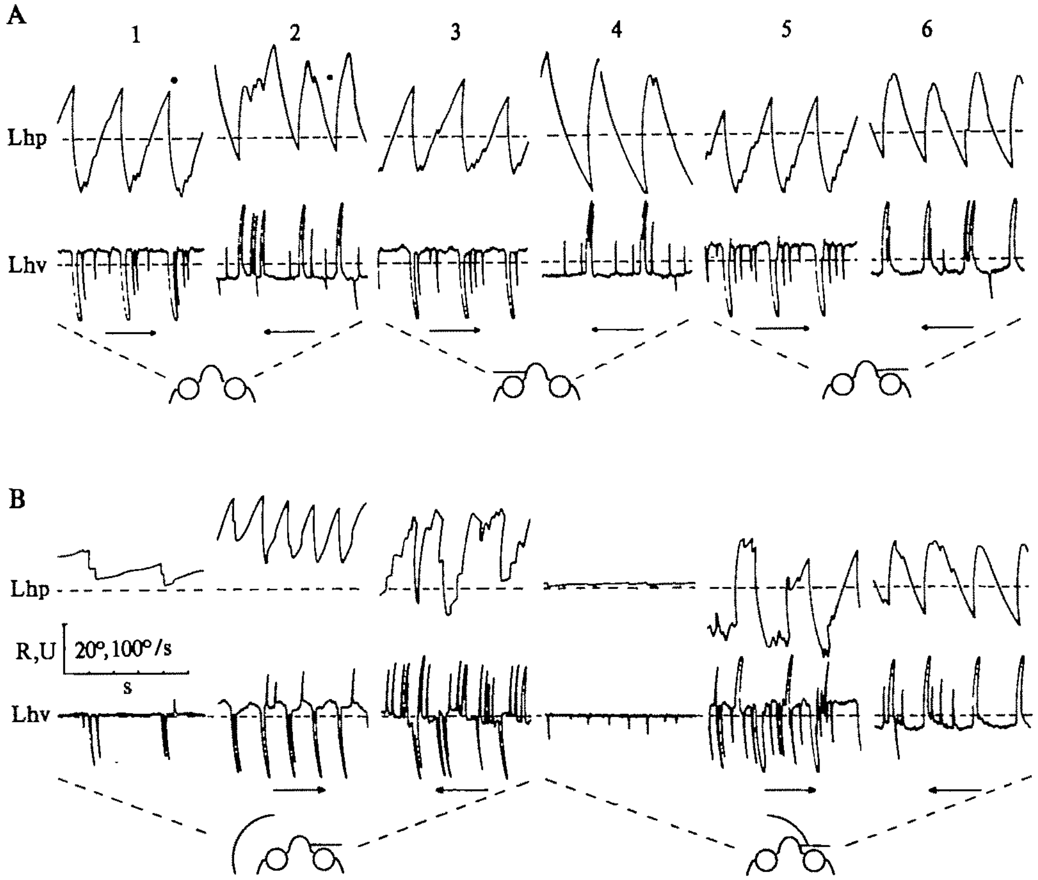

FIG. 13. Class III OKN elicited with binocular and monocular full-field and monocular half-field stimulation for Case 16. A, binocular (left two columns), right eye (middle columns), and left eye (right two columns) OKN induced by a full-field (hemicylindrical screen), rightward or leftward (*see* arrow direction) target motion (stripes drifting at 30 deg/s). Both binocular and monocular OKN show gains close to 1.0 and are also symmetrical with regard to direction of target motion. B, spontaneous nystagmus to a stationary target and OKN with left eye viewing elicited by stimulation of the right visual field, i.e. temporal hemiretina of the left eye (first three columns) or left visual field stimulation, i.e. nasal hemiretina of the left eye (last three columns). For the static target, temporal hemiretinal stimulation shows more nystagmus (up to 5 deg/s, *see* column 1) than static target stimulation of the nasal hemiretina (column 4). OKN responses of the temporal hemiretina are erratic with target motion leftward (column 3). In contrast, OKN responses from the nasal hemiretina are excellent with a gain of up to unity. Response asymmetry noted indicates that the temporal hemiretina cannot mediate smooth following in the temporal direction.

components elicited in this condition consisted of drift towards the midposition (fig. 13, lower trace, column 3; fig. 14, column 5). With stimulation of the nasal retina alone, regular OKN was elicited in both directions with variable gains. Spontaneous nystagmus with a stationary target in Case 16 (fig. 13, columns 1 and 4) was stronger during exposure of the temporal rather than the nasal retina. These findings suggest a specific defect of temporal pursuit in the temporal retina (nasal visual

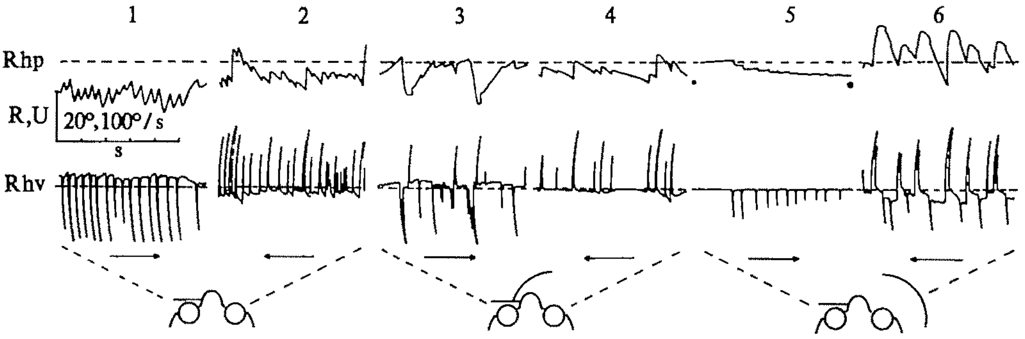

FIG 14. OKN elicited with monocular full-field and half-field stimulation for Class III subject, Case 14. Full-field monocular OKN for rightward (column 1) or leftward (column 2) target motion (tangent screen, grating drifting at 47 deg/s) is fairly symmetrical. Right visual field stimulation of the right eye, i.e. nasal hemiretina (columns 3 and 4) shows relatively good responses with a gain of 0.20 for rightward target motion and 0.11 for leftward target motion. Left visual field stimulation of the right eye, i e. temporal hemiretina (columns 5 and 6) shows a poor response for rightward (temporal) target motion with a gain of 0.01; gain for leftward (nasal) target motion is higher, up to 0.46. The asymmetry seen here is similar to that seen for Case 16 (*see also* fig. 13) For both subjects, the temporal hemiretina shows abnormal temporally directed smooth eye movements.

field). No defect of this type was observed in any of the 10 normal subjects studied by Van Die and Collewijn (1982) under similar conditions. In Case 15 half field stimulation did not elicit reliable responses. Vertical OKN was tested only in this subject: it was comparable to her horizontal OKN (gain 0.44 up, 0.55 down).

DISCUSSION

The two most likely causes underlying oculomotor instability in albinism are (1) foveal abnormalities which result in degraded sensorimotor feedback, or (2) optic pathway anomalies which result in directional errors of sensorimotor feedback. Arguments in support of the first alternative rely upon the fact that nystagmus is also a common feature of nonalbino disorders such as aniridia and congenital achromatopsia (Waardenburg, 1970), in which foveal hypoplasia and poor fixation are primary features. Although impaired acuity may contribute to the intensity of the nystagmus, the difficulty in designating an abnormal neural retina as the presumptive cause of albino nystagmus is at least two-fold. First, the neonate is born with an immature retina. That is, adult-like macular and foveal differentiation and resultant retinal function are not reached before 4 months postnatally (Mann, 1949; Abramov *et al.*, 1982). Since albino nystagmus is purported to be present at birth or within the first 3 months of age (Johnson *et al.*, 1971; O'Donnell and Green, 1979), it is difficult to explain how an immature retinal ganglion cell and receptor substrate with poor resolving capacities (Weale, 1982; De Vries-Khoe and Spekreijse, 1982) are responsible for the early onset of oculomotor instability. Although this counterargument holds for a causal relationship between nystagmus

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and impaired image processing, a possible role of the immature retina causing nystagmus as a result of other aberrant neural processes, for example aberrant nasal and temporal retinal ganglion cell organization, cannot be excluded. Secondly, despite the fact that foveal hypoplasia, as indicated in part by an absent foveal reflex, is an obligate albino feature, nystagmus is not (Krill, 1977; Hornabrook *et al.*, 1980).

In this light it seems more fruitful to hypothesize that misrouted visual projections are the primary cause of the oculomotor instability. As the misrouting affects the fibres which normally have an ipsilateral destination and originate in the temporal retina, the most serious defects might be expected to be found in association with the use of the nasal parts of the visual field. This is certainly the case for the albino rabbit, which offers a relatively simple model for the ocular instability (Collewijn *et al.*, 1978). The rabbit has lateral eyes with monocular visual fields extending only about 15 deg across the midline (Hughes, 1971). In the pigmented rabbit, ipsilaterally projecting ganglion cells are confined to a 3.0 to 3.5 mm wide strip adjacent to the temporal retinal margin, whereas contralaterally projecting ganglion cells are present throughout the whole retina (Provis and Watson, 1981). A basically similar situation exists in the pigmented rat (Cowey and Perry, 1979). In this rodent the uncrossed optic fibres originate from a temporal retinal sector with a width of about 40 deg, but after midsagittal section of the optic chiasma these uncrossed projections are unable to mediate optokinetic following (Cowey and Franzini, 1979). These findings show that in pigmented rabbits and rats the projections of the temporal retina are bilateral and that the role of the ipsilateral projections in OKN is questionable.

Albino rabbits usually have stable eyes when vision is unrestricted, but spontaneous nystagmus and inverted OKN are unmasked when only the temporal retina is exposed to a structured pattern. This demonstrates two principles: (1) the abnormal response is primarily associated with the temporal retina; (2) there is a trade-off between normal and disorganized visual field sectors. Since the temporal retinal sector which projects ipsilaterally is small in the rabbit, it is obvious that inverted OKN responses originating from this sector in the albino mutant will be overwhelmed by the preponderant, normally connected nasal retina. The borderline between the normal and inverted OKN was found about 30 deg anterior to the interocular axis (Collewijn *et al.*, 1978). This suggests that the inverted sector is larger than the one covered in the normal animal by the ipsilaterally projected retinal zone.

Defects of OKN have also been noted in other albino species with lateral eyes. With full field stimulation, OKN was found to be absent in albino rats (Precht and Cazin, 1979). This could be an effect of mutual cancelling of the input from normal and inverted visual field sectors, as has been shown for hypopigmented mice (Mangini *et al.*, 1982). Similar to the situation in the rabbit, in these mice normal OKN was found with the anterior visual field masked whereas inverted OKN resulted when the temporal retina was stimulated, as in the rabbit.

The neurophysiological basis of the inversion of the rabbit's OKN is not entirely clear. One possibility is a sign error in velocity-coded signals. About one quarter of the rabbit's retinal ganglion cells has direction-selective properties (Oyster, 1968). One channel through which these project is the nucleus of the optic tract (NOT), which appears to be the main relay station for visual information controlling the rabbit's OKN (Collewijn, 1975). In the albino rabbit, Winterson and Collewijn (1981) found that the receptive fields of single NOT units were normally organized posteriorly, but had an inverted direction preference in the parts more anteriorly than about 30 deg, in agreement with the oculomotor behaviour. The inverted OKN and the convergence of normal and inverted direction-selective signals onto single NOT neurons would be most simply explained by aberrant crossing of direction-selective fibres from the temporal retina. Recent anatomical investigations have not supported this theory, as ipsilateral retinal projections to the NOT have not been found in either pigmented or albino rabbits (Takahashi and Oyster, 1980; Klooster *et al.*, 1983; Collewijn and Holstege, 1984). This does not eliminate the possibility that direction-selective fibres with other ipsilateral destinations (e.g. the superior colliculus or the lateral geniculate nucleus) cross in the albino rabbit and aberrantly innervate the contralateral NOT.

Another possibility is that the site of the inversion is more peripheral: direction-selective elements in the retina might be wrongly coded. An anomalous retinal organization would not necessarily be restricted to the most temporal parts; this could cause the large extent of the inverted zone in many albino rabbits.

Not much is known about specific abnormalities of the albino rabbit's retina. Choudhury (1981) has reported a reduced number of ganglion cells and lack of a concentration of large ganglion cells in the temporal retina. However, single unit studies of albino retinal ganglion cells are not available.

The Siamese cat offers an attractive model of albinism in a frontal-eyed species. In the normal cat, the decussation line separating the contralaterally projecting nasal retina from the ipsilaterally projecting temporal retina is rather sharp, at least for the retinogeniculate projection (Cooper and Pettigrew, 1979*a*). By studying cats with a sagittally transected chiasma or a sectioned optic tract (Precht *et al.*, 1980; Montarolo *et al.*, 1981) it has been established that both crossed and uncrossed retinal fibres are also to mediate OKN in both temporonasal and nasotemporal directions, with a slight directional preference of the nystagmus for the crossed fibre system in the nasal direction and for the uncrossed fibres in a nasotemporal direction. That the gain of the OKN was subnormal is probably due to the reduced number of retinofugal fibres. In the monkey uncrossed fibres also are capable of generating OKN (Pasik and Pasik, 1964). For man, the role of ipsilateral and contralateral projections can be inferred from experiments with selective stimulation of various retinal sectors (Van Die and Collewijn, 1982). Monocular stimulation of each half retina induces OKN in either direction, with a lower gain than for full-field stimulation and with a slight preference for motion towards the retinal centre, in agreement with the findings mentioned above for the cat.

Unfortunately, the control of eye movements in Siamese cats has not been studied in any detail except that it is known that many of them have strabismus; spontaneous nystagmus has not been described. On the other hand the retinal origin of crossed and uncrossed fibres and the deformations of the cortical retinotopical maps have been carefully documented. The retinal decussation line is not only shifted to the temporal side but also smeared out so that the transition from total contralateral to total ipsilateral projection takes place over a distance of 6 mm, as compared to the 0.8 mm extent in the normal cat (Cooper and Pettigrew, 1979*b*). If more or less similar relations exist in human albinos, then less than half of the retinal ganglion cells has anomalous connections, but this sector includes the central part of the temporal retina. As shown by Van Die and Collewijn (1982) the central retina largely controls human OKN.

The aberrant crossing fibres are connected to the wrong hemisphere and give rise to disorganized cortical maps. The anomalous inflow gives rise to an inverted segment, which could potentially generate inverted oculomotor control signals. However, the situation is highly complex because for the Siamese cats it has been shown that the anomalous inputs are either suppressed ('midwestern' type) or partly rearranged into a normal sequence ('Boston' types), with a mixture of these variants as a further possibility (*see* Hubel and Wiesel, 1971; Guillery *et al.*, 1974; Cooper and Blasdel, 1980).

For human pursuit and OKN the cortical pathway is of overwhelming importance and in contrast to the rabbit most evidence indicates that subcortical pathways are ineffective in generating OKN (*for review see* Collewijn, 1981). If the dominant oculomotor control signals are derived from a cortex which receives input signals out of order or even inverted, the emergence of inverted or chaotic oculomotor responses seems an unavoidable consequence.

In view of the individual variability among albino rabbits and Siamese cats it should be no surprise that albino humans show large differences in oculomotor behaviour. Small changes in the number of misrouted fibres could determine the majority of normal or inverted connections, resulting in stable or unstable eyes. In addition the cortical processing of the anomalous inflow may vary individually, with either suppression or rearrangement, as in Siamese cats.

Our Class III subjects are virtually stable and have normal pursuit and OKN. Even monocular OKN was symmetrical (fig. 15) and lacked the preference for pursuit in the nasal direction often associated with degraded binocular vision (Schor and Levi, 1980; Van Hof-van Duin and Mohn, 1982) and seen also in one of our Class I subjects (fig. 7). The defect of pursuit in the temporal direction using the temporal retina suggests a mild dysfunction of the connections from the temporal retina.

For Class I subjects we suppose that the anomalous information is effectively processed and also overwhelms normal signals. This may turn the normally negative visuomotor feedback loop into an unstable positive feedback loop. A target movement will elicit an opposite eye movement and any eye movement with respect to a stationary stimulus will create the stimulus for its own continuation. These are run away responses in which the 1 : 1 relation between input and output is entirely lost. Experiments with long-term masking in albino rabbits (Collewijn *et al.*, 1980) indicate that the brain, at least in the rabbit, is incapable of correcting this type of instability; the resulting spontaneous nystagmus will continue indefinitely. The predominantly horizontal character of the nystagmus fits well with a decussation anomaly. If foveal maldevelopment were the primary cause of nystagmus, it would be hard to explain why vertical stability would be maintained. In a recent model of the generation of congenital nystagmus waveforms, Optican and Zee (1984) have also proposed positive velocity feedback as one of the causes of ocular instability. As they have pointed out, the inappropriate velocity feedback might be derived from sources other than the retinofugal fibres, such as extraocular muscle proprioceptors or an efference copy.

Inversion is most purely shown in our Class II subjects, who reliably inverted the direction of their nystagmus under the influence of an optokinetic stimulus. This is often described as a typical sign of congenital nystagmus (*see* Halmagyi *et al.*, 1980). Although it was present in only 2 of our albino subjects, we found the same phenomenon in 1 nonalbino subject with spontaneous (probably congenital) nystagmus. The inversion was sometimes present during pursuit as well. Wildberger and Meyer (1978) recorded inverted OKN in 2 of their 10 albino subjects. It therefore seems safe to conclude that systematic inversion of OKN is seen only in a minority of human albinos. Selective retinal stimulation did not identify the temporal retina as its origin and the nystagmus continued in darkness.

We conclude that although misrouting of retinofugal projections appears to be one likely cause of spontaneous nystagmus in human albinism, no simple model emerges at present which can account for this abnormality in all its variability.

ACKNOWLEDGEMENTS

The authors wish to thank Drs J. W. Delleman and D. Van Dorp for their kind collaboration and all the albino subjects for their helpful participation.

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(*Received April 3, 1984. Revised July 12, 1984. Accepted July 17, 1984*)

Brain (1985), **108**, 29–41

PATTERN AND EXTENT OF DEMYELINATION IN THE OPTIC NERVES OF MICE INFECTED WITH SEMLIKI FOREST VIRUS AND THE POSSIBILITY OF AXONAL SPROUTING

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SUMMARY

The optic nerves of all mice infected with Semliki Forest virus (SFV) showed patchy demyelination, although the extent of demyelination varied between animals. There was a significant increase in small diameter unmyelinated fibres in the optic nerves of SFV infected mice, paralleled by a loss of small myelinated fibres, suggesting that the smaller myelinated fibres may be more susceptible to virus-induced demyelination. The small unmyelinated fibres were more numerous in the peripheral region of the optic nerve trunk, where blood vessels are found in greater numbers. In addition, a particularly large increase in the proportion of unmyelinated fibres which had diameters of less than 0.2 μm suggested the possibility of axonal sprouting.

INTRODUCTION

Many light and electron microscopical studies on the cerebellum and medulla of Swiss A^2G mice infected with Semliki Forest virus (SFV) have described the occurrence of demyelination caused by this infection (*see* Chew-Lim *et al.*, 1977, 1978; Pathak and Webb, 1978; Suckling *et al.*, 1978; Illavia *et al.*, 1982; Kelly *et al.*, 1982), but no information is available concerning the proportion of infected mice which develop patchy demyelination in the CNS or the proportion of the nerve fibres in a given neural pathway that are likely to become demyelinated. As the degree of functional deficit in SFV-infected mice has been determined by electrophysiological techniques comparable to those used for diagnostic purposes in man (Tremain and Ikeda, 1983), it was of interest to correlate the degree of physiological deficit observed with morphological evidence of the site and extent of demyelination. This paper describes a quantitative study of the pattern and extent of virus-induced demyelination in the optic nerves of albino mice.

In an electron microscopic study of the pathological changes in the optic nerves of SFV-infected mice, Illavia *et al.* (1982) described demyelinated fibres, macrophages with phagosomes containing myelin debris, hypertrophied astrocytic processes and phagocytic oligodendrocytes. Our preliminary electron microscopic study (Fleming *et al.*, 1982) confirmed these observations. However, recent studies of axonal transport in optic nerves in SFV-infected mice (Pessoa and Ikeda, 1984) produced results which require a fresh examination of the electron microscopic appearances. Although the rate of transport was not changed, the amounts translocated by both fast and slow axonal transport were significantly increased in the optic nerves of SFV-infected mice when compared with controls. Since an increase in axonal transport in injured nerves has been shown to be associated with axonal sprouting (Wolburg, 1981; McQuarrie and Grafstein, 1982), it appeared pertinent to examine the optic nerves of SFV-infected mice for evidence of the presence of axonal sprouts. We therefore looked specifically for evidence of unusually small diameter axons, and have quantified their incidence, in an attempt to correlate the results of the earlier axonal transport studies with our present anatomical observations.

METHODS

Inoculation Procedure

The procedure for inoculating mice (St Thomas' Hospital Medical School strain of albino mice originally bred from Swiss A^2G mice) has been described in detail elsewhere (Tremain and Ikeda, 1983; Pessoa and Ikeda, 1984). Forty control mice received a dose of 0.1 ml of bovine albumin in phosphate-buffered saline (BAPS) intraperitoneally at both 4 and 6 weeks of age and 40 experimental mice received a dose of 0.1 ml avirulent Semliki Forest virus (SFV) in BAPS intraperitoneally at both 4 and 6 weeks of age.

Histological Preparation

Throughout the histological processing, embedding, sectioning and staining of the optic nerves, specimens taken from control and infected mice have been treated as matched pairs. Six to ten days after the second inoculation, the mice were deeply anaesthetized with pentobarbitone sodium (Sagatal, May and Baker, 60–65 mg/kg i.p.) and the brain and the optic nerves were removed rapidly and fixed in 3 per cent glutaraldehyde in 0.1 M phosphate buffer, pH 7.4 for 3 h at 4° C. Perfusion fixation was not performed because of the technical difficulties inherent in attempts to obtain reproducible perfusion in such small animals and immersion fixation is an accepted procedure for small pieces of tissue of less than 0.5 mm diameter (Glauert, 1975). After washing with Sörensen's buffer, the nerves were postfixed in buffered 1 per cent osmium tetroxide for 1 h, again at 4° C, before dehydration in graded ethanols. Nerves taken from control and infected mice will be referred to as control and infected nerves.

Control and infected nerves from littermates were paired and embedded together in Araldite. For light microscopy, 1 μm thick transverse sections of the paired nerves were cut at 300 μm intervals and stained with 1 per cent toluidine blue in 1 per cent borax. For electron microscopy ultrathin transverse sections of 3 pairs of nerves were stained with a saturated ethanolic solution of uranyl acetate and 0.3 per cent aqueous solution of lead citrate. The sections were viewed in a JEOL 120 CX electron microscope at 80 kV.

Microdensitometric Assessment of Demyelination

Myelin is the principal component stained in resin-embedded optic nerves stained with toluidine blue. As the control and infected nerves had been processed, sectioned and stained as pairs, it was considered that the relative staining intensity of the members of each pair could provide one measure of the extent of demyelination in the infected nerves. A Vickers M86 scanning and integrating microdensitometer was therefore used to scan each of the paired nerve sections, 3 scans 60 deg apart being made across the diameter of each nerve, as shown in fig. 1. Along each of the 3 scanning lines, a 20 μm^2 measurement area was chosen at 6 positions, 1 at each peripheral end of the scan, 2 at the centre of the nerve trunk and 2 points at a midway position on each radius (marked as P, C and M in fig. 1). The densitometer determined the absorption of light at 550 nm wavelength in each 20 μm^2 area. The results are expressed in arbitrary units of relative absorption.

Morphometric Techniques

One optic nerve was taken from each of 3 control and 3 infected animals. The animals were all littermates, inoculated and killed at the same time. Thus 3 matched control and infected nerve pairs were processed histologically as pairs throughout, although they were eventually embedded in separate blocks for sectioning. The nerve sections were picked up on rhodium-coated 200 mesh copper Maxtaform grids of 3 mm diameter and one cross-section of each nerve was selected at a distance of approximately 200 μm from the optic nerve head. Two sets of electron micrographs were taken at right angles across the diameter of each optic nerve trunk (i.e. 2 scans per nerve, *see* fig. 2).

Between 18 and 20 nonoverlapping photographs were taken in succession along each of the 2 scans, and thus 36 to 40 photographic prints at a final magnification of ×24900 were available from each nerve for the counting and measurement of myelinated and unmyelinated fibres. Micrographs from each scan were divided into 6 regions, 2 representing the periphery, 2 the centre and 2 a midway position along the radius of the nerve.

In each enlarged photograph, the external diameters of all myelinated (including the myelin sheath) and unmyelinated fibres were measured with a millimeter ruler. For fibres with an irregular ouline, measurements were made of the smallest and largest diameters and these were averaged. These methods are similar to those employed by Honjin *et al.* (1977) in their extensive analysis of over 60000 optic nerve fibres in the mouse. Fibres were counted and measured only if more than 75 per cent of their cross-section was included in the micrograph.

Particular attention was paid to the identification of very small diameter axons which might represent sprouts. These were required to fulfil the following criteria: (1) a mean axon diameter of less than 0.2 μm; (2) a clearly defined and continuous plasma membrane; (3) cytoplasm with the structural

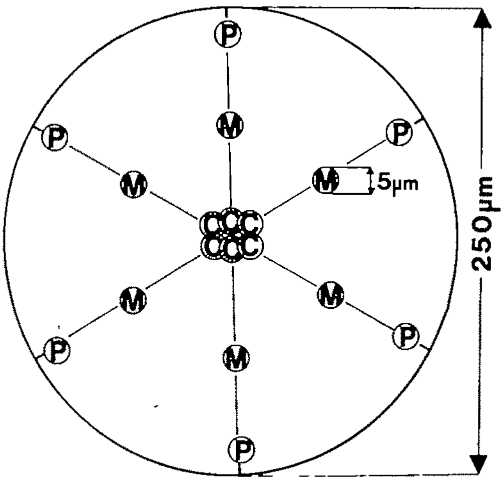

FIG. 1. Densitometry protocol for the optic nerve. Positions at which the microdensitometry measurements were made in each pair of transversely sectioned optic nerves (one nerve from a control and the other from an SFV-infected mouse). Each measurement area: 20 μm^2. C = centre; M = midway; P = periphery of the optic nerve trunk.

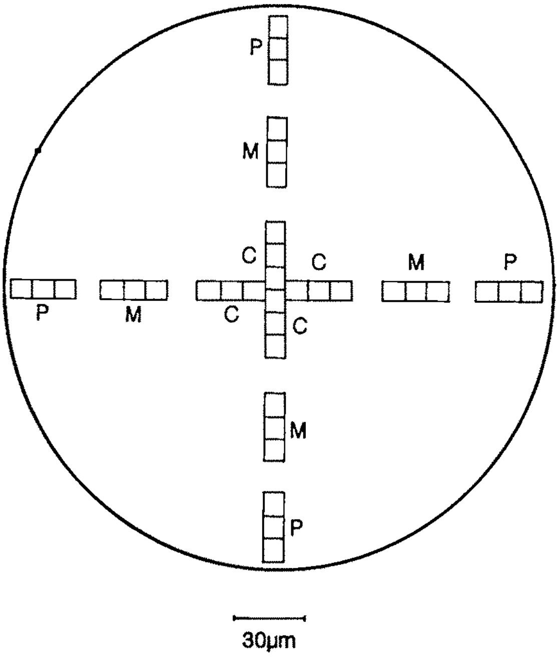

FIG. 2. Protocol of photomicrographs taken in succession along the vertical and horizontal axes of a transverse section from 3 pairs of control and infected optic nerves. These photographs were used for the measurement of myelinated and unmyelinated fibre size and also for the identification of axonal sprouts. Lettering as in fig. 1.

characteristics of axoplasm (Landon, 1981); and (4) a nearly circular outline without any acute angle to the limiting membrane, clearly detached from any neighbouring myelin sheath. The fourth criterion was applied in order to differentiate possible axonal sprouts from oligodendrocyte processes.

RESULTS

Density of Myelin Staining in Paired Control and SFV-infected Optic Nerves—Quantification of Demyelination

Fig. 3 shows a low power micrograph of transverse sections of 2 optic nerves, 1 from a control mouse and the other from a mouse infected with SFV, processed as a pair. The control nerves were invariably more densely stained than the infected nerves, and the latter frequently possessed a halo-like appearance. This was caused by the presence of a pale annular area at the periphery of the nerve trunk, surrounding the darker central zone, suggesting that demyelination was more extensive at the periphery. Fig. 4A shows the results of microdensitometry performed on one such pair of nerves. All points obtained from the control nerve exceeded those obtained from the infected nerves. The difference between the staining density was greatest at the periphery of the nerve trunk, although, as can be seen from the figure, a difference was still detectable at the centre.

The measurements undertaken on the 10 pairs of control and infected optic nerve sections are combined in fig. 4B. Six readings were taken at each point on each section; the mean value is thus based on 60 sampling measurements. Since the

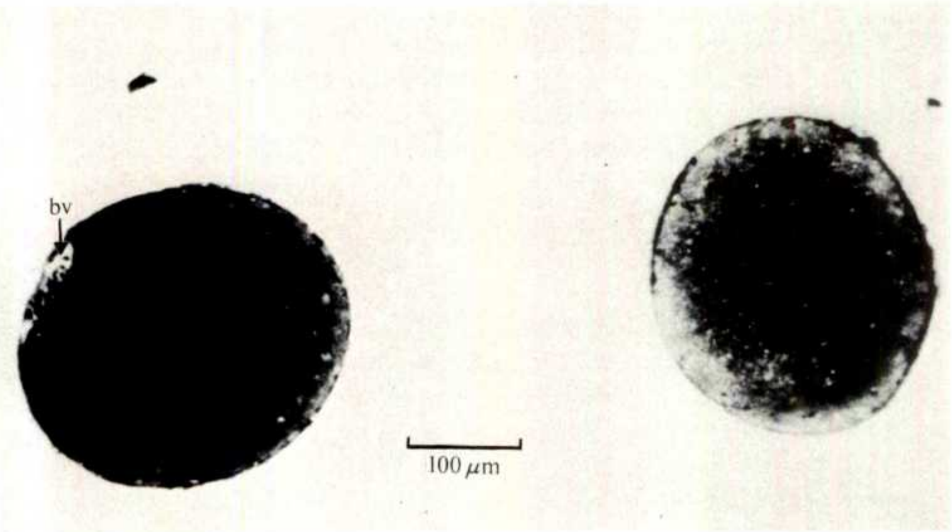

FIG. 3. Light micrographs of transverse sections from one pair of optic nerves, toluidine blue stain. The left is taken from a control mouse and the right from a mouse infected with SFV; bv = blood vessel.

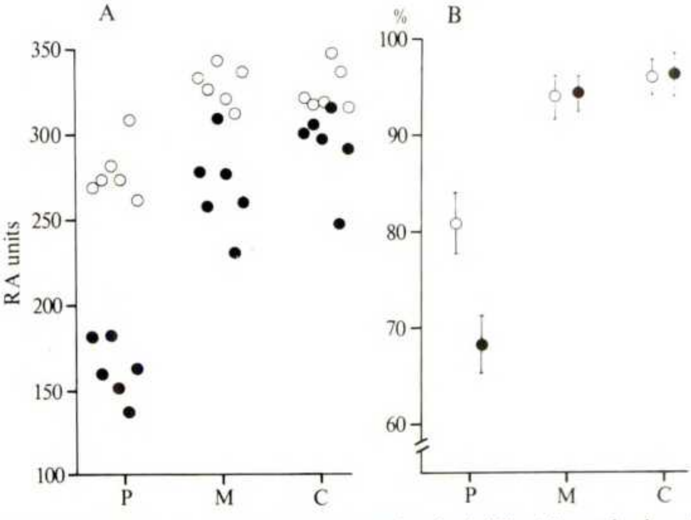

FIG. 4. A, microdensitometric measurements from one pair of toluidine blue-stained optic nerves showing relative absorption (RA units) at 550 nm taken at peripheral (P), midway (M) and central (C) positions; open circles = control nerves; closed circles = infected nerves. B, means and standard errors of the 10 pairs studied; 100 per cent on the Y axis was the maximum relative absorption value obtained in any one pair. Open circles = controls; closed circles = infected.

absolute values of the light absorbed varied from one pair of nerves to another the ordinate is now expressed as relative percentage absorption, taking the maximum absorption in each pair as 100 per cent. In both control and infected nerves, there was a tendency for the centre of the nerve to be more darkly stained than its periphery. The mean difference observed between the control and the infected nerves was significant in the peripheral zone ($P < 0.001$) but not for the centre and middle zones.

Fibre Numbers and Diameters

Both myelinated and unmyelinated fibres were counted on photomicrographs taken across 3 pairs of control and infected nerve sections. The results are given in Table 1 which shows that there are considerably more unmyelinated fibres in the infected nerves. When the totals for all 3 nerves are combined, the percentage of unmyelinated fibres in the infected nerves (28.3%) is almost four times that of the control nerves (7.6%).

TABLE 1. NUMBERS AND PERCENTAGES OF MYELINATED (M) AND UNMYELINATED (U) FIBRES IN EACH OF THE THREE PAIRS OF NERVES EXAMINED

	Controls			*Infected*		
Pairs	*Total*	*M*	*U*	*Total*	*M*	*U*
1	1105	1055	50	1524	1315	209
		95.5%	4.5%		86.3%	13.7%
2	1642	1484	158	1096	464	632
		90.4%	9.6%		42.3%	57.7%
3	1547	1429	118	1509	1180	329
		92.4%	7.6%		78.2%	21.8%
Totals for all 3 nerves	4294	3968	326	4129	2959	1170
	100%	92.4%	7.6%	100%	71.7%	28.3%

Fig. 5 shows the results of the measurements of myelinated and unmyelinated fibre diameters. The distributions are shown in 0.2 μm units, with the exception of those below 0.5 μm and those above 2.1 μm in diameter where the data are grouped. The range of diameters was found to be broadly similar in the control and infected nerves, but there is an apparent shift to the right in the peak of the histogram of the myelinated fibre groups in the infected nerves. This may suggest that some of the smaller myelinated fibres have become demyelinated and now appear in the histograms of the unmyelinated fibre group. The total number of the fibres counted in the 3 control nerves was 4294 and 4129 in the 3 infected nerves.

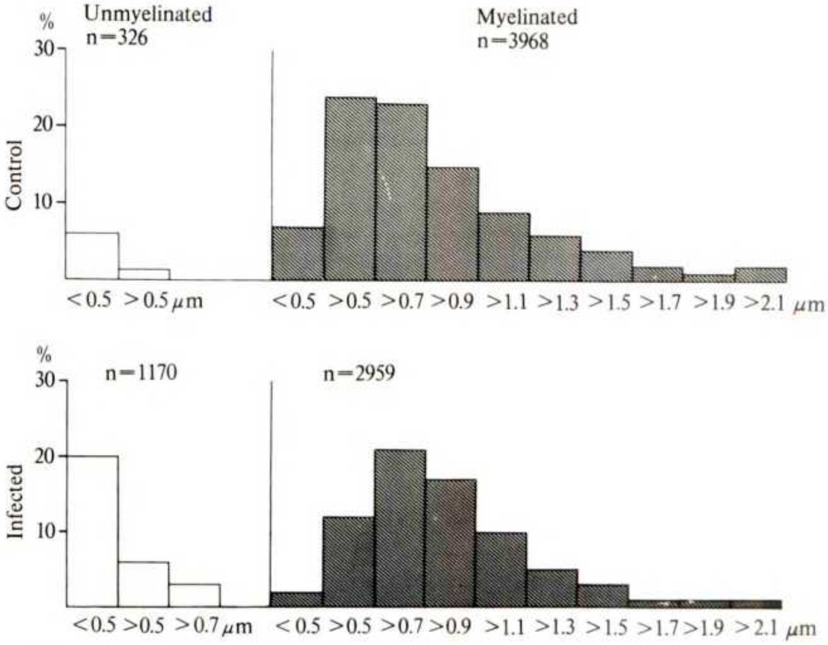

FIG. 5. Percentage size-frequency distributions for unmyelinated and myelinated fibres in the optic nerves of the control (4294 fibres; 3 nerves) and infected mice (4129 fibres; 3 nerves).

Table 2 shows the percentages of unmyelinated fibres counted and measured at the peripheral, intermediate and central portions of the optic nerve trunk in the 3 control and infected nerve pairs. There is a considerable increase in the proportion of unmyelinated fibres in each region of each infected nerve when compared with the corresponding region of its control nerve. The increase is most marked in the

TABLE 2. UNMYELINATED FIBRES AT EACH OF THE THREE SITES SAMPLED, EXPRESSED AS PERCENTAGES OF THE TOTAL NUMBER OF FIBRES FOUND AT THE PERIPHERY, MIDPOINT AND CENTRE

		Periphery		*Midpoint*		*Centre*	
Pairs		*Control*	*Infected*	*Control*	*Infected*	*Control*	*Infected*
1	% unmyelinated	5.9% (n = 373)	23% (n = 521)	6.2% (n = 356)	9.3% (n = 494)	1.6% (n = 376)	8.5% (n = 509)
2	% unmyelinated	8.9% (n = 503)	69.1% (n = 385)	11.6% (n = 480)	59.5% (n = 304)	8.5% (n = 659)	45.5% (n = 407)
3	% unmyelinated	8.9% (n = 415)	26.6% (n = 496)	10.1% (n = 516)	22.7% (n = 519)	4.7% (n = 616)	16.0% (n = 494)
Total no. of unmyelinated fibres		104	518	130	345	92	307
Unmyelinated		8.1% (n = 1291)	37% (n = 1402)	9.6% (n = 1352)	26.2% (n = 1317)	5.6% (n = 1651)	21.8% (n = 1410)

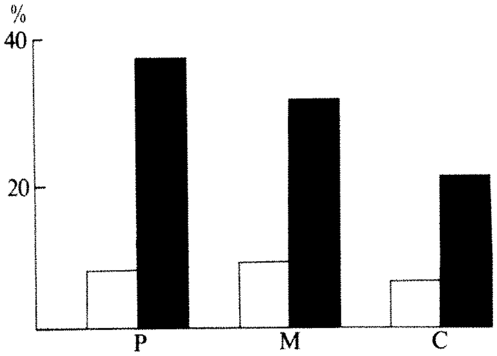

FIG. 6. Percentages of unmyelinated fibres found in each of the 3 regions sampled. P = periphery; M = midway (midpart of the radius) and C = centre of the optic nerve trunk from the 3 pairs of control (open columns) and infected mice (solid columns).

periphery of all 3 infected nerves. This effect is shown more clearly in fig. 6 where the unmyelinated fibres from all 3 control nerves and all 3 infected nerves are plotted as percentages of the total number of fibres counted in each region.

Axonal Sprouting

Since an increase in the proportion of small (< 0.5 μm diameter) unmyelinated axons was a noticeable feature of the infected nerves, the electron micrographs were re-examined to identify and quantitate the presence of unmyelinated axons of less than 0.2 μm diameter, using the criteria defined in the Methods section. This may indicate axonal sprouting.

Fig. 7 shows examples of micrographs taken from transverse sections through part of the peripheral zone of an infected nerve. Fig. 7A illustrates the appearance and relative sizes of the myelinated and unmyelinated axons and the astrocytic processes. These unmyelinated axons were not associated with any morphological evidence of pathological change. The profiles of the unmyelinated axons were clearly distinguishable from those of the myelinated axons sectioned through their nodes, examples of which are shown in fig. 7B. Fig. 7C shows a further example of a cluster of small diameter unmyelinated axons including some below 0.2 μm in diameter (arrowed), which were identified as 'sprouts'. The results of counts of such possible axonal sprouts are shown in fig. 8. The infected nerves contained almost four times as many 'sprouts' as did the control nerves, the increase being particularly pronounced at the periphery of the nerve trunk.

DISCUSSION

The results described above are interpreted to indicate that the optic nerve fibres of mice infected with Semliki Forest virus (SFV) undergo demyelination. Two lines of evidence lead to this conclusion. The densitometry technique was used to determine the proportion and distribution of myelin, on the assumption that the majority of the staining intensity in a nerve can be attributed to its content of myelin.

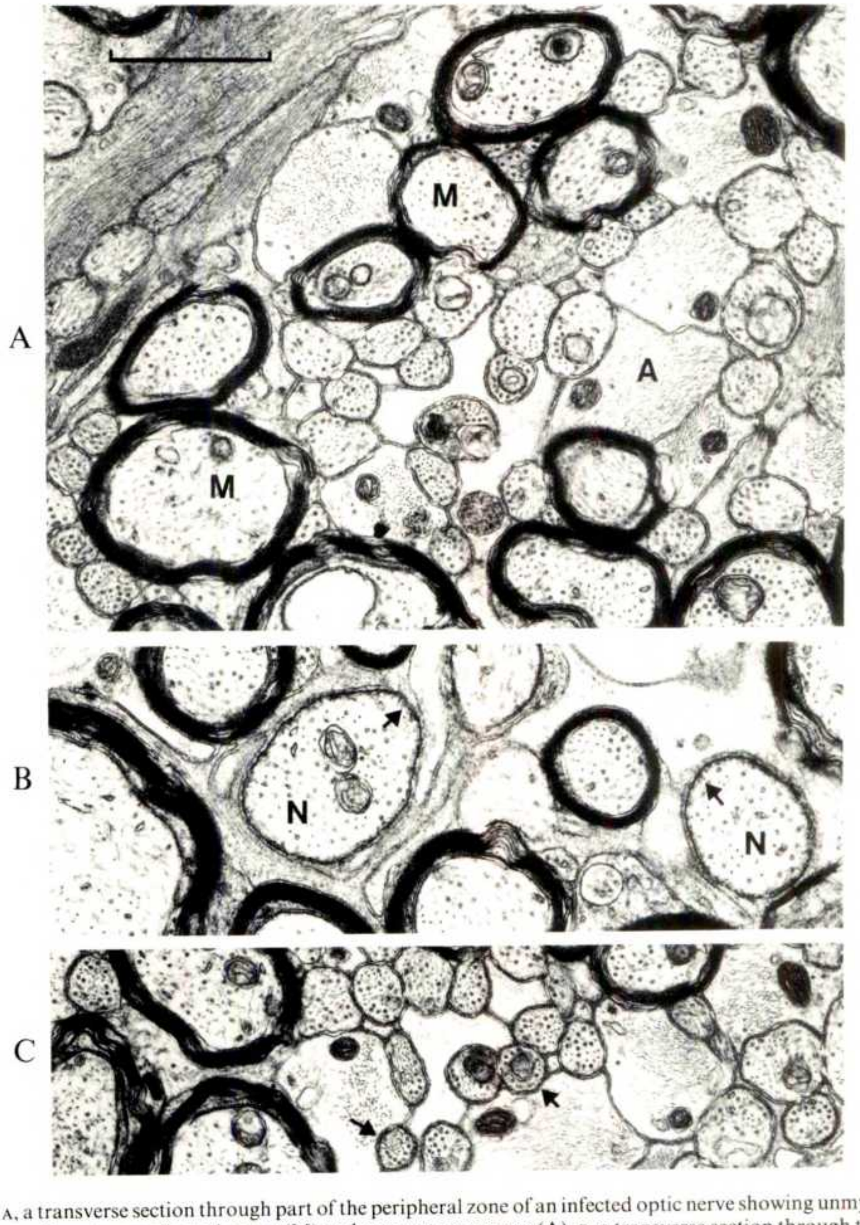

FIG. 7. A, a transverse section through part of the peripheral zone of an infected optic nerve showing unmyelinated axons, larger diameter myelinated axons (M) and astrocyte processes (A). B, a transverse section through the nodes of Ranvier of two myelinated axons (N). They are distinguishable from the small unmyelinated axons in A by their larger diameter and the densely stained undercoating beneath the axolemma (*arrows*). C, a further example of a collection of small diameter axonal profiles identified as sprouts (*arrows*). Scale = 1 μm.

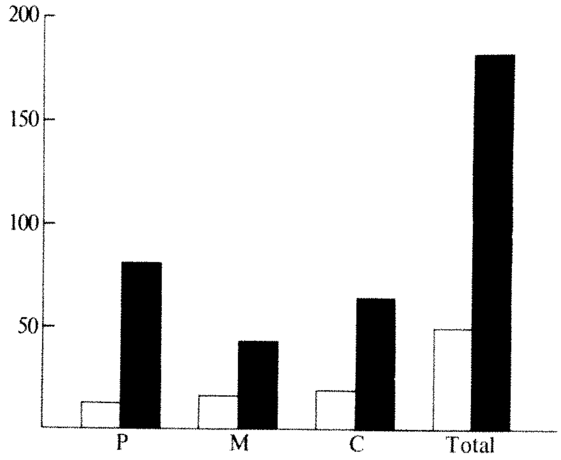

FIG. 8. Numbers of fibres fulfilling the criteria for 'sprouts' (*see text*) in the samples from the peripheral (P), midway (M) and central (C) regions of the optic nerves of control (open bars) and infected (filled bars) mice.

Although this assumption ignores the possibility that the contribution of other structures which take up toluidine blue may be included in the measured optical density, we believe that it is a useful technique for comparing the overall myelin content of control and infected nerves that have been prepared as a pair throughout. The densitometer results showed that there was less myelin in the infected nerves, and that this loss was more pronounced at the periphery was confirmed and extended by the quantitative analysis of electron micrographs.

Secondly, in each of the 3 pairs of control and infected nerves examined there was an increase in the number of unmyelinated fibres in the infected nerve as compared with its control. The proportion of unmyelinated fibres ranged from 13.7 per cent (in pair 1) to 57.7 per cent (in pair 2) and emphasized the considerable individual variation found in the degree of demyelination. This finding suggests that factors other than genetic composition, environment and nutritional status can affect the susceptibility of an animal to SFV infection.

We found that the increase in the incidence of unmyelinated fibres was restricted to the lower end of the axon diameter range (fig. 6). Demyelination may thus preferentially affect smaller rather than large axons, in turn raising the possibility that the small myelinated fibres themselves are more susceptible to virus-induced demyelination, even if some allowance is made for the possibility that some reduction in axon diameter may follow demyelination. The susceptibility of smaller optic nerve fibres to demyelinating conditions may be relevant to the clinical observation that optic neuritis associated with MS often involves the papillo-macular fibres, thus causing a central scotoma (McDonald, 1975; Harms, 1976; Meadows, 1976). Those arising from the fovea or macula are the smallest among the optic nerve fibres, originating from the smallest retinal ganglion cells (Polyak, 1941; Stone and Johnston, 1981).

The considerably greater proportion of unmyelinated fibres in the peripheral zone of infected optic nerves requires explanation. The capillary network of mouse optic nerve is poorly developed, the blood supply being derived from several arterioles that arise from the anterior cerebral artery and run forward along the nerve itself (Honjin *et al.*, 1977). In the optic nerves examined in our studies, many large blood vessels were noted in the periphery of the nerve trunk. Although the pathogenesis of demyelination in SFV infection is controversial (Sheahan *et al.*, 1981; Dal Canto and Rabinowitz, 1982), it has been suggested that passage of the virus into mouse brain occurs across the capillary endothelium (Pathak and Webb, 1974). This could allow more virus to be deposited in sites with a relatively rich blood supply (Chew-Lim *et al.*, 1978), as appears to be true for the periphery of the optic nerve. Perivascular demyelination in viral infections has some precedents. Thus in infection with canine distemper virus (Wiśniewski *et al.*, 1972) and Theiler's virus (Dal Canto and Lipton, 1975), demyelination is often observed around blood vessels.

Finally, in relation to our finding of possible axonal sprouting in the infected nerves (figs. 7 and 8), it is known that in the mammalian CNS some axons are capable of regrowing and forming collaterals after injury (Bernstein and Bernstein, 1971; Bowen *et al.*, 1975; Matthews *et al.*, 1976; Duce and Keen, 1980; Field, 1980). Previous reports have shown that optic nerve demyelination is accompanied by an increase in fast axonal transport and some nerve fibre regeneration (Wolburg, 1981; McQuarrie and Grafstein, 1982), and a significant increase in both fast and slow axonal transport has been found in the optic nerves of SFV-infected mice (Pessoa and Ikeda, 1984). The identification of the small unmyelinated axonal profiles found in the infected nerves as 'axon sprouts' remains speculative. Although these structures might represent a proliferation of fine longitudinally orientated oligodendrocyte processes generated as part of the response to SFV infection or demyelination, in our view this is unlikely. Alternatively, they might be atrophic axons which have suffered a gross reduction in calibre as a consequence of demyelination but such a phenomenon has never been described previously in other experimental demyelinating lesions in the CNS (Harrison *et al.*, 1972; Blakemore, 1973; Ludwin, 1981). Thus the most plausible explanation for the presence of numerous small diameter cylindrical structures with a morphology indistinguishable from axons, occurring in clusters in the infected optic nerve, is that they have an analogous significance to similar structures described in regenerating unmyelinated peripheral nerves and represent new axonal outgrowths or 'sprouts' (Ochoa, 1976). How this phenomenon relates to the pathology of the SFV infection and, specifically, whether these sprouts represent regrowth following previous axonal degeneration, or additional sprouts from intact or demyelinated axons, remains to be determined.

In conclusion, our results indicate that demyelination occurs in the optic nerves of SFV-infected mice, predominantly affecting small diameter fibres and particularly those at the periphery of the optic nerve trunk where large blood vessels are present. This may be accompanied by axon sprouting. The mechanisms responsible for both the demyelination and the axon sprouting are at present obscure.

ACKNOWLEDGEMENTS

This work was supported by grants from the Multiple Sclerosis Society of Great Britain and from the Special Trustees of St Thomas' Hospital to H.I. We thank Dr H. Webb for the gift of SFV and useful discussions, Mr T. Allen for computing assistance and Mrs G. Blake for help in the preparation of the manuscript.

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(*Received March 15, 1984. Revised May 15, 1984. Accepted June 29, 1984*)

Brain (1985), **108,** 43–63

A QUALITATIVE LIMITATION ON VISUAL TRANSFER *VIA* THE ANTERIOR COMMISSURE

EVIDENCE FROM A CASE OF CALLOSAL AGENESIS

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SUMMARY

Interhemispheric transfer of visual information was investigated in a patient with agenesis of the corpus callosum. CT scanning, pneumoencephalography, and neuropsychological evaluation failed to reveal any evidence of extracallosal cortical damage. The patient's performance was within normal limits both in the left and right visual fields on tasks requiring identification of briefly presented material. In contrast, his performance was abnormally poor when required simply to detect or localize a dot presented to the right of fixation. Performance with presentations in the left visual field was normal. These findings suggested that the absence of the corpus callosum may result in a selective impairment of visuospatial, but not identification, processes for material initially presented to the left hemisphere. To document this possibility further, the patient was tested on tasks designed to assess these processes simultaneously by requiring him both to identify and judge the exact location of each stimulus presented. Performance was normal in both lateral fields for identification accuracy, but significantly worse in the right visual field for location judgements. A similar pattern of results was found on a task requiring the identification of a stimulus and specification of its spatial orientation.

These findings suggest a qualitative limitation on the type of information which may be transferred *via* the anterior commissure, possibly due to the inability of temporal lobe neurons to encode spatially organized information. Furthermore, the findings suggest that in the normal brain the right hemisphere may be crucially involved in visual attention and spatial functions, regardless of the field of presentation.

INTRODUCTION

Studies of commissurotomy patients by Sperry, Gazzaniga and colleagues have documented the critical role of the neocortical commissures in mediating interhemispheric transfer of visual information in man. Perhaps the clearest and most dramatic effect of this surgical procedure is the inability of these patients to report verbally material briefly presented in the left visual field (LVF) (e.g. Gazzaniga *et al.*, 1965). In marked contrast, lateral visual field studies of patients with agenesis of the corpus callosum have found no comparable evidence of disconnection (*see* Milner and Jeeves, 1979, for review). Logically, this discrepancy could be accounted for in two ways: (1) by postulating that one consequence of callosal agenesis is the development of bilateral speech, thereby negating the necessity for interhemispheric transfer, or (2) that acallosal individuals use other pathways for transferring visual information.

Evidence in support of the bilateral speech hypothesis is scant, and may be considered inconclusive at best. The two reported attempts to verify speech lateralization directly in an acallosal subject using carotid amylobarbitone (Amytal) injection revealed bilateral speech in one case (a left-handed female, Saul and Gott, 1973), and unilateral speech in the other case (B. Milner, as reported by Gazzaniga, 1970, p. 138). Studies employing indirect measures of speech lateralization (e.g. dichotic listening tasks) have been equally inconclusive. For example, acallosal subjects have been reported to have a right ear advantage (e.g. Jeeves, 1965), a left ear advantage (e.g. Lassonde *et al.*, 1981) and a smaller ear difference than found in normal individuals (e.g. Ettlinger *et al.*, 1974; *see* Chiarello, 1980, for a review of these studies and a discussion of the difficulties in interpreting dichotic listening data with regard to speech lateralization). Furthermore, while the bilateral speech hypothesis may account for the verbalization of material presented in the LVF, it cannot account for accurate performance by acallosal subjects on tasks requiring cross integration of information delivered simultaneously in both lateral fields (e.g. Sperry, 1970; Ettlinger *et al.*, 1974).

Evidence in favour of the alternative hypothesis, namely mediation of visual transfer *via* other pathways, is somewhat more compelling. In the Bogen and Vogel population of 'split-brain' subjects all the neocortical commissures were severed surgically. In addition to the corpus callosum this included the hippocampal commissure and the anterior commissure (Bogen and Vogel, 1962). In contrast, in the most common type of callosal agenesis the corpus callosum and hippocampal commissure are absent but the anterior commissure is present and often found to be hypertrophied (Lemire *et al.*, 1975).

The anterior commissure, normally situated below the rostrum of the corpus callosum, interconnects anterior regions of the temporal lobe both directly and indirectly *via* the amygdala (Klinger and Gloor, 1960). Combined electrophysiological and lesion studies of subhuman primates have demonstrated that temporal lobe areas involved in visual processing receive some information from the ipsilateral visual field *via* this pathway (Gross *et al.*, 1977). In addition, behavioural studies of monkeys with resection limited to the corpus callosum have demonstrated near perfect levels of performance on pattern recognition tasks necessitating interhemispheric transfer of visual information (e.g. Sullivan and Hamilton, 1973). Furthermore, visual transfer has been found to occur in at least some human patients with resections limited to the corpus callosum (Risse *et al.*, 1978). Therefore, although there have been reports of apparently total visual disconnection in man after resection of only the posterior extent of the corpus callosum (Gazzaniga and Freedman, 1973; Damasio *et al.*, 1980; McKeever *et al.*, 1981), there is also ample evidence to suggest that, at least under certain conditions, the anterior commissure may mediate information exchange. However, for those cases in which direct cortical interaction is assumed to be limited to the anterior commissure, it has not been clearly determined whether there are any limitations, either quantitative or qualitative, to visual information transfer *via* this pathway.

In the following series of studies an attempt was made to explore this issue in a subject with verified agenesis of the corpus callosum. In the past, perhaps the greatest difficulty for interpreting the data from these patients has been the presence of extracallosal cortical damage, and concomitant behavioural abnormalities, commonly found in association with callosal agenesis (e.g. Loeser and Alvord, 1968; Chiarello, 1980). The case reported here is unique in this regard due to a lack of evidence of any cortical abnormalities not directly related to the absence of the corpus callosum. It will be argued that the limitations in visual transfer in this patient are consistent with a model which assumes normal intrahemispheric organization of functions with direct hemispheric interaction limited to the anterior commissure.

CASE REPORT

The patient, G.B., a 22-year-old right-handed male, was diagnosed as suffering from Shapiro's syndrome, a disorder characterized by episodic hyperhidrosis, hypothermia and agenesis of the corpus callosum (Shapiro and Plum, 1967; Shapiro *et al.*, 1969; Noël *et al.*, 1973; Sadowsky and Reeves, 1975; Carr-Locke and Millac, 1977). Neuropathological findings have been reported for one case. Only the most rostral section of the corpus callosum was present. The anterior commissure was intact and enlarged (Noël *et al.*, 1973).

The patient had normal developmental, neurological and medical histories until the age of 21 years when he began to have attacks of profuse sweating. When admitted to the National Institutes of Health (NIH) these attacks were occurring two to eight times per day and lasting from 5 to 30 min each. Average body temperature was 33.3° C. An EEG revealed diffuse slowing with no focal abnormalities. Approximately one month after admission he suffered three brief generalized seizures. The patient responded well to anticonvulsant medication (phenobarbitone) and during the ensuing weeks his body temperature returned to the normal range with no recurrence of sweating attacks or seizures. No EEG abnormalities were noted at this time. A full neurological case history of this patient is given by LeWitt *et al.* (1983).

Total agenesis of the corpus callosum was verified by a CT scan and pneumoencephalogram (figs. 1 and 2). There was no evidence of hydrocephalus, nor of any cortical or subcortical abnormalities other than those directly related to the absence of the corpus callosum (e.g. dorsal dilatation of the third ventricle).

General intellectual abilities, as assessed by the Wechsler Adult Intelligence Scale (Wechsler, 1955), were in the normal range. This test was administered when G.B. was still having attacks of hyperhidrosis with abnormally low body temperature and therefore probably represents a low estimate of his true abilities. Performances on neuropsychological tests of memory, language, visual perceptual and constructional abilities, and perceptual-motor functioning were all within normal limits (*see* Table 1).

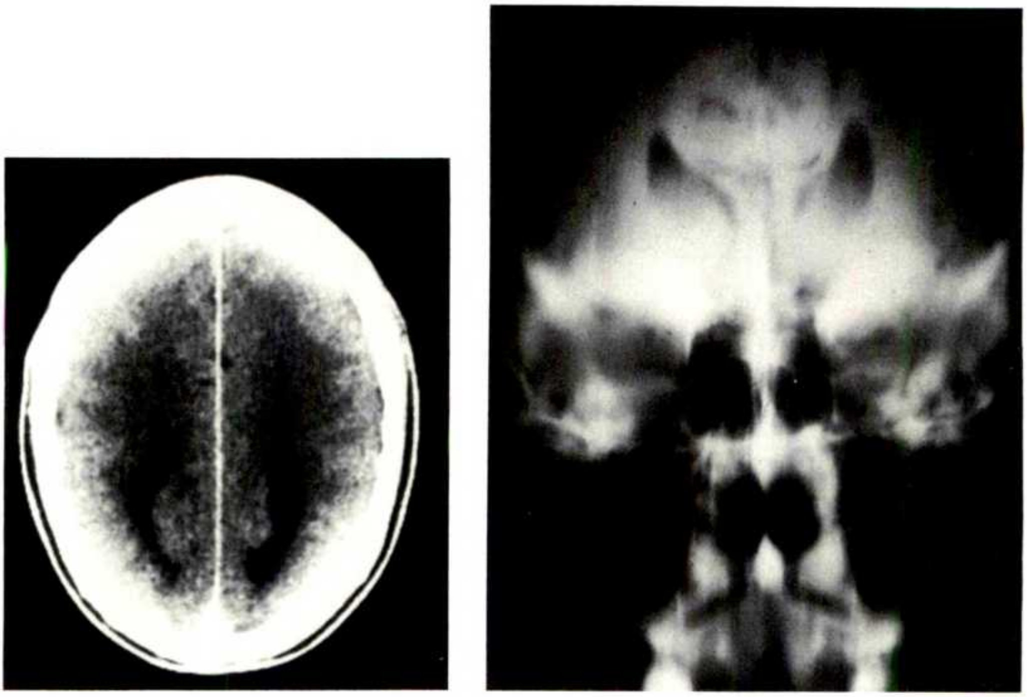


FIG. 1 (*left*). CT scan at the level of the lateral ventricles showing complete absence of the corpus callosum. FIG. 2 (*right*). Pneumoencephalogram showing 'bat wing' appearance of the lateral ventricles typically seen in cases of callosal agenesis.

Auditory verbal processing was assessed under two conditions, monaural-alternating and dichotic. G.B. was tested on two separate occasions, approximately two weeks apart. During both sessions G.B. displayed a right ear advantage and bilateral supression when switching from monaural alternating to dichotic presentation, as is often found with normal individuals (Berlin and McNeil, 1976) (*see* Table 2).

In summary, the patient was asymptomatic before the onset of attacks of recurrent hyperhidrosis and hypothermia. No indications of extracallosal cortical damage was revealed by a pneumoencephalogram or CT scan. Performance was well within normal limits on a variety of tests of neuropsychological functions. In addition, performance on a dichotic listening test provided no basis for assuming abnormal speech lateralization in this patient. G.B. therefore represented an ideal candidate for examining interhemispheric transfer of visual information in the absence of the corpus callosum. The observations to be reported were obtained while G.B. was on phenobarbitone and his body temperature remained within the normal range.

EXPERIMENTS

The patient participated in seven experiments, each run on a separate day. For comparison purposes 6 right-handed males of similar age (range 21 to 26 years) and education as G.B. served as controls.

TABLE 1. PSYCHOMETRIC PROFILE

Function	*Test*	*Score*	*Percentile*[1]
General intellectual abilities	Wechsler Adult Intelligence Scale[2]		
	Verbal IQ	93	32nd
	Performance IQ	99	47th
	Full Scale IQ	95	37th
Memory	Wechsler Memory Scale[3]		
	Memory Quotient	97	42nd
Verbal	Story recall	20/46	58th
Nonverbal	Visual reproduction	11/14	50th
Language			
Naming	Boston Naming Test[4]	71/85	42nd
Comprehension	Token Test[5]	160/163	44th
Visual perception and reasoning	Ravens Coloured Progressive Matrices[6]	34/36	77th
Visuoconstructive ability	Rey-Osterrieth Complex Figure Test:[7] Copy	35/36	87th
	Block Design (WAIS)	36/48	63rd
Perceptual-motor ability	Purdue Peg Board[8]		
	Right hand	16	WNL[9]
	Left hand	13	WNL
	Both hands	12	WNL

[1] Percentiles based on published normal data. [2] Wechsler (1955). [3] Wechsler and Stone (1945). [4] Kaplan *et al.* (1976). [5] Spreen and Benton (1969). [6] Raven (1956). [7] Osterrieth (1945). [8] Costa *et al.* (1963). [9] WNL = within normal limits.

TABLE 2. AUDITORY PERCEPTION UNDER MONAURAL-ALTERNATING AND DICHOTIC CONDITIONS[1]

	Alternating[2]		*Dichotic*[3]		*% suppression*[4]	
	L ear	*R ear*	*L ear*	*R ear*	*L ear*	*R ear*
Session 1	47	70	27	35	43	50
Session 2	53	70	42	46	21	34

[1] Percentage correct recall of words delivered to the left (L) and/or right (R) ears of patient G.B. [2] Twelve six-word trials were presented. Words were separated by an interval of 500 ms, delivered alternately to the L and R ear. [3] Twenty-four six-word trials were presented. Words were matched on the basis of initial phoneme, delivered simultaneously to the L and R ear. [4] Computed by Alternating-Dichotic/Alternating.

Performance was evaluated statistically in two ways. First, absolute level of accuracy in each visual field was tested by computing Z scores based on the performance of the normal subjects. Secondly, the magnitude of the difference (Zdz), between the visual fields was evaluated according to the procedure of Payne and Jones (1957) for investigating a single case. The abnormality of the discrepancy between visual fields was tested by the formula:

$$\mathrm{Zdz} = \frac{\mathrm{Zx} - \mathrm{Zy}}{\sqrt{(1+1-2r_{xy})}}$$

where x = RVF, y = LVF and r = correlation.

Informed consent was obtained from the patient and control subjects under an existing research protocol approved by the NIH. It was explained to all participants that these studies were for research purposes only and neither the patient nor the normal volunteers were informed of specific results.

Identification

The majority of studies of lateral visual field perception with commissurotomy and acallosal patients, as well as with normal individuals, have required subjects to identify briefly presented stimuli either by naming or recognizing them from among an array of similar material. The patient was first tested on three tasks of this type.

Procedures

All stimuli for the following studies, as well as for all others to be reported, were presented *via* a four channel Gerbrands tachistoscope (model T-4A). For successive presentation tasks, stimuli were presented in random order to the left and right visual fields (LVF and RVF), the only constraint being a maximum of three consecutive trials in the same visual field. Each trial began with the presentation of a central fixation cross for 2 s immediately followed by a lateralized stimulus.

Experiment 1: word reading, unilateral-successive presentation. Stimuli consisted of 24 three-letter words, written vertically in upper case letters. Each word was lateralized 2 deg 24 min from fixation and subtended a visual angle of 1 deg 55 min in the vertical plane. Three blocks of 24 trials, (12 per field) were presented at durations of 100, 50 and 25 ms on successive blocks. Subjects were instructed to report verbally the word presented.

Experiment 2: word reading, bilateral-simultaneous presentation. The procedure and stimuli were the same as those employed in Experiment 1 except that on each trial two different words were presented positioned 3 deg 42 min to the left and right of fixation. Four blocks of 12 trials were run at durations of 150, 100, 75 and 50 ms on successive blocks. Subjects were instructed to report both words in any order.

Experiment 3: random shape recognition, unilateral-successive presentation. The 24-point random shape stimuli developed by Vanderplas and Garvin (1959) were employed. The shapes were lateralized 3 deg 42 min measured from their geometric centre to fixation and subtended a visual angle of approximately 1 deg 51 min vertically and horizontally at their greatest extent. The stimulus set consisted of fifteen different shapes, each appearing twice in each visual field for a total of 60 trials. Two blocks of 30 trials were presented at durations of 20 and 15 ms, respectively. After each presentation the subject was presented with a response card placed in free view which contained the target stimulus and five distractor items and was instructed to point to the shape he had seen.

Results and Discussion

On all three tasks G.B. performed within the normal range on both LVF and RVF presentations (*see* fig. 3). Relative to normals, the patient's poorest performance was for word reading in the LVF on Experiment 1 ($Z = 1.74$, $P = 0.08$). This, however,

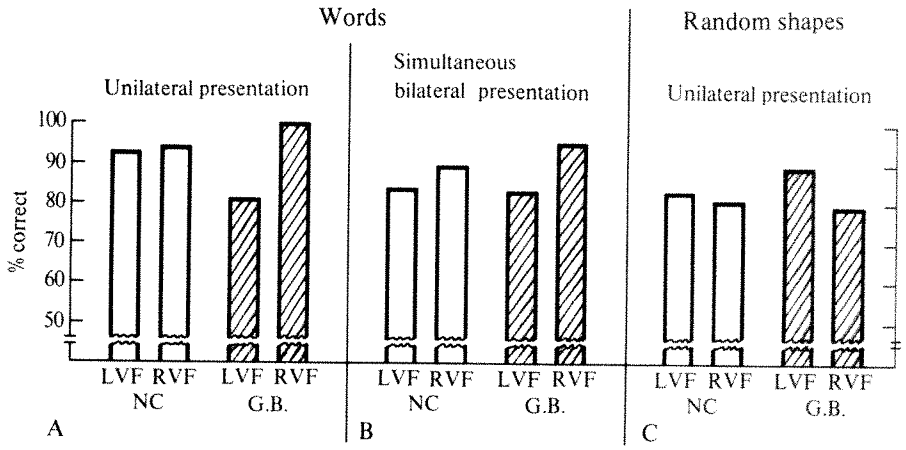


FIG. 3. Mean percentage correct responses in the LVF and RVF for normal control subjects (NC) and G.B. on three identification tasks. A and B are for word reading, C is for recognition of random shapes; A and C, unilateral presentation, B, simultaneous bilateral presentation. Data were averaged across all blocks of trials in each experiment.

resulted from his misreading of 5 of the first 12 words presented in this field. Only two additional errors occurred for the following 24 LVF presentations, even though these trials were run at considerably shorter exposure durations. The computed measure of discrepancy between visual fields failed to reach significance for this study ($Zdz = 1.81$, $P = 0.07$), for bilateral simultaneous word reading ($Zdz = 1.22$, $P > 0.10$), or shape recognition ($Zdz = 0.86$, $P > 0.50$).

It should be noted that the patient's performance was similar to that of normal individuals in two important ways. First, he showed a high degree of accuracy in identifying (reading and recognizing) material presented in the lateral visual fields. Secondly, he exhibited the expected visual field asymmetries, namely, a slight RVF advantage for word reading under both successive and simultaneous presentations, and a slight LVF advantage for matching complex random shapes. The RVF advantage for word reading, together with the right ear advantage on dichotic listening, is consistent with, and suggestive of, normal lateralization of speech to the left hemisphere. If so, then it can be assumed that this patient is demonstrating efficient interhemispheric transfer of visual information.

Dot Detection and Localization

In contrast to tasks requiring identification or recognition, other tasks may be presented for which the identity of the stimulus is irrelevant for correct performance. For example, independent of the question of 'what is it?' we may ask 'is something present?' and further 'where is it?' and 'how is it orientated?'.

Studies with normal individuals on such tasks have yielded equivocal results with respect to hemispheric asymmetry. For example, on dot detection tasks, Kimura (1969) and Bryden (1976) failed to find a significant visual field asymmetry, while Davidoff (1977) and Allard and Bryden (1979) reported significant detection advantages in favour of the LVF. On tasks requiring exact localization of briefly presented dots a significant LVF advantage was found by Kimura (1969) and Levy and Reid (1978) but not by Pohl *et al.* (1972), Bryden (1976) or Allard and Bryden (1979). Similarly, a significant visual field advantage, again in favour of the LVF, was found on tasks requiring judgement of line orientation by Fontenot and Benton (1972) and Kimura and Durnford (1974), but not by White (1971).

While in no way representing a consistent body of evidence, it should be noted that the majority of studies have reported either a significant or nonsignificant trend in favour of the LVF (*see* Davidoff, 1977 for review). This is of interest since neglect and inattention to contralateral space have been noted to occur more often after damage to the right than to the left hemisphere (e.g. Critchley, 1953; Costa *et al.*, 1969; Albert, 1973; Colombo *et al.*, 1976), and patients with right, but not left, posterior lesions have been found to be impaired on tasks of dot localization (Taylor and Warrington, 1973; Hannay *et al.*, 1976) and line orientation (Warrington and Rabin, 1970; Benton *et al.*, 1975). Since direct cortical interaction between posterior regions is mediated *via* the corpus callosum it was of interest to assess how the acallosal patient would perform on such tasks.

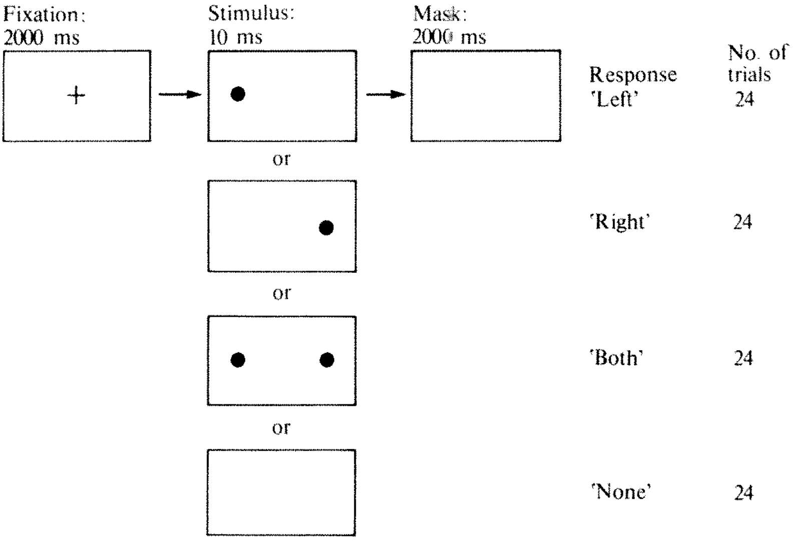
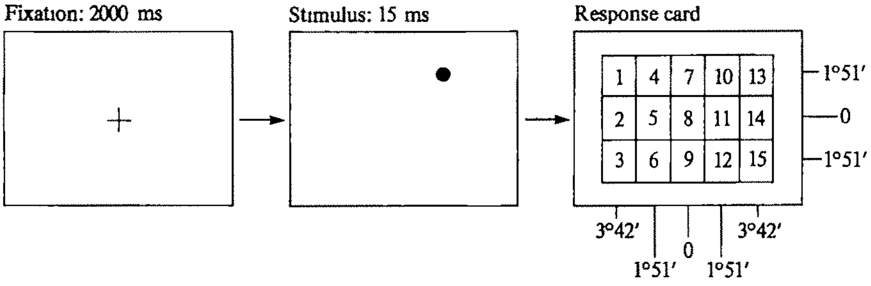


FIG. 4. Trial sequence for dot detection. Procedure for assessing detection sensitivity in the lateral visual fields. The dots subtended a visual angle of 28 min of arc, lateralized 3 deg 42 min from fixation point.

Procedures

Experiment 4: dot detection. The trial sequence and stimulus characteristics are illustrated in fig. 4. In order to reduce uncertainty about location, the bilateral card was exposed first and the subject was told that the dots would appear only in these two positions. By alerting the subject to the possibility of simultaneous bilateral presentations, detection sensitivity could be evaluated for both visual fields on each trial. For example, if a subject responded 'left' to the left dot card he was credited with a hit for the LVF and a correct rejection for the RVF. Similarly, a response of 'left' to the bilateral card was scored as a hit for the LVF and a miss for the RVF; a response of 'both' to the right dot card was scored as a hit for the RVF and a false alarm for the LVF, etc. Due to uncertainty about the distributions of signal and noise under these conditions, and since a relatively small number of trials were run, a nonparametric measure of sensitivity was used as suggested by Bryden (1976). This measure, P(Ā), takes into account the observed proportions of hits and false alarms to provide an estimate of the area under the ROC curve (McNichol, 1972).

Experiment 5. dot localization. Trial sequence and stimulus characteristics are illustrated in fig. 5. The response card remained visible until the subject responded. Visual field differences were assessed by tabulating exact localizations for positions in the two lateral columns on each side of the response grid (i.e. positions 1 to 6 and 10 to 15, *see* fig. 5).



Correct response '10'

FIG. 5 Trial sequence for dot localization (90 trials, 6 per cell) Procedure for assessing dot localization accuracy in the lateral visual fields.

Results and Discussion

Dot detection. G.B. was tested twice with approximately two weeks between sessions (*see* fig. 6). The normal subjects demonstrated relatively high accuracy in both visual fields with a slight, but nonsignificant trend towards better detection in the LVF ($t(5) = 1.94$, $P > 0.10$). For the acallosal subject, however, there was a dramatic difference in performance in favour of the LVF. While G.B.'s ability to detect the dot when it was presented in the LVF was clearly unimpaired, his score for the RVF fell outside the normal range during both sessions 1 and 2. More importantly, on both sessions the difference between visual fields for G.B. was significantly larger than the mean visual field difference for normal subjects ($Zdz = 3.69$, $P < 0.001$ for session 1; $Zdz = 4.53$, $P < 0.001$ for session 2). The false alarm rate was relatively low and equal in the LVF and RVF for both normal individuals and the acallosal subject (LVF = 6.4%, RVF = 5.0% for normals;

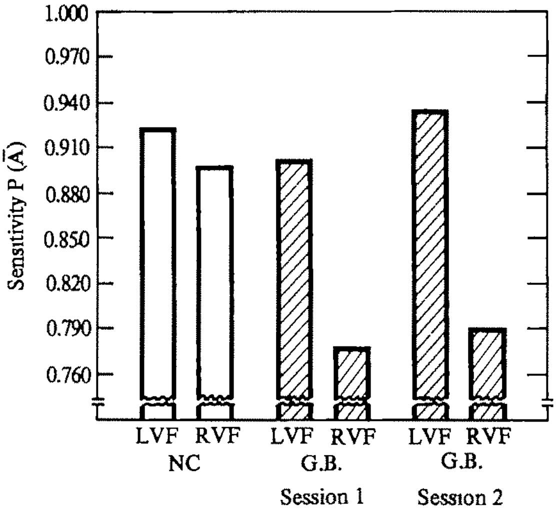


FIG. 6. Dot detection. Mean detection sensitivity scores in the LVF and RVF for normal control subjects (NC) and G.B.

LVF = 6.25%, RVF = 6.25% and LVF = 6.25%, RVF = 8.33% for G.B. on sessions 1 and 2, respectively). Thus G.B.'s relatively poor performance with RVF presentations was apparently not the result of a response bias, but instead reflected a true hemifield difference in detection sensitivity.

Dot localization. The same pattern of results was found on the dot localization task (*see* fig. 7). Exact localizations were calculated in two ways. First, by determining the percentage of correct localizations in each visual field and secondly, by computing the measure of sensitivity, P(Ā), to correct for any response bias for particular locations.

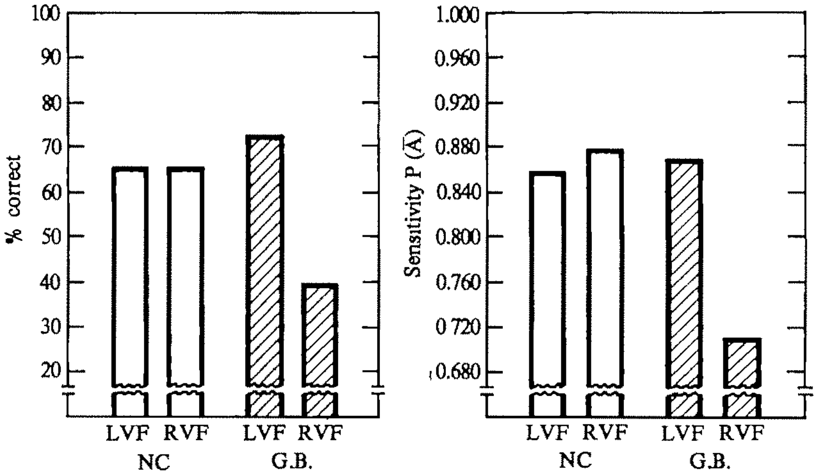


FIG 7. Dot localization. Mean percentage correct localizations and localization sensitivity in the LVF and RVF for normal control subjects (NC) and G.B.

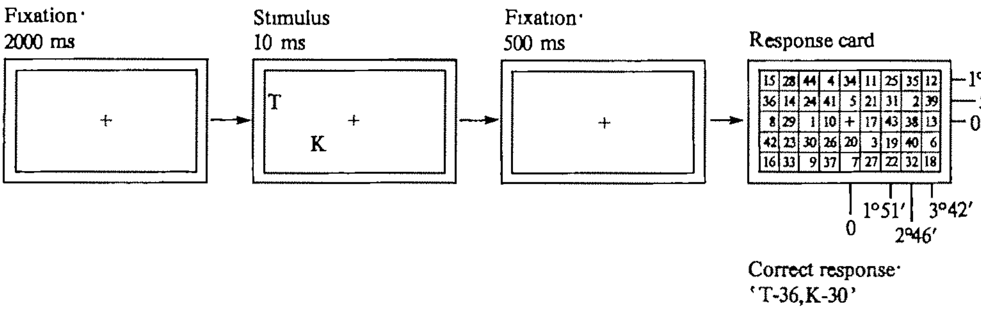
The normal subjects exhibited a slight, nonsignificant, advantage in favour of the RVF using both scoring procedures ($t(5) = 1.0$ for percentage accuracy and $t(5) = 1.1$ $P > 0.10$, for localization sensitivity). As in the dot detection task, G.B.'s performance was within the normal range for the LVF, but clearly defective in the RVF ($Z = 2.70$, $P < 0.01$ for percentage accuracy; $Z = 4.54$, $P < 0.001$ based on the localization sensitivity scores). Furthermore, the discrepancy between the visual fields for G.B. was significantly larger than that observed for normal individuals ($Zdz = 2.00$, $P < 0.05$ and $Zdz = 4.13$, $P < 0.001$ for percentage accuracy and localization sensitivity, respectively). There were no significant visual field differences in false alarm rate for normal subjects (LVF = 12.5%, RVF = 10.3%), or for G.B. (LVF = 13.9%, RVF = 16.7%), and G.B. did not differ from normals in either field on this measure of bias.

On the previous identification tasks the acallosal subject was found to be indistinguishable from normal individuals with respect both to overall level of accuracy and the discrepancy between visual fields. In contrast, an abnormally large discrepancy between fields emerged when detection and localization were required. Furthermore this discrepancy was solely due to poor performance on RVF presentations. Taken together, these results suggested the possibility of a selective impairment in spatial analysis, but not identification, of material initially presented to the left hemisphere. Since this hypothesis is based on comparisons between different procedures, administered at different times, tasks were developed to simultaneously assess these processes.

Letter Localization and Word Orientation

Procedure

Experiment 6 letter localization. The sequence of events presented on each trial is illustrated in fig. 8. In an attempt to increase localization accuracy, a frame, corresponding with the border of the response grid, was included on the fixation card, and a fixation cross was included on the response card. The fixation card was presented at a slightly reduced illumination relative to the stimulus card and remained visible during stimulus presentation so that the letters appeared superimposed within a

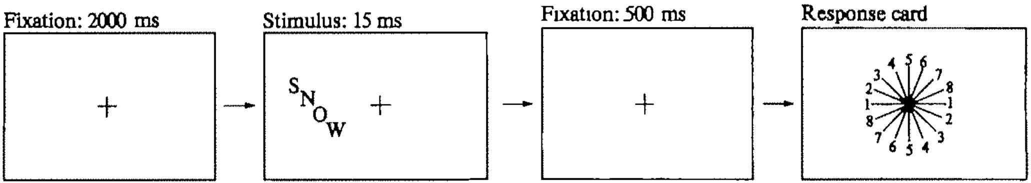


15	28	44	4	34	11	25	35	12
36	14	24	41	5	21	31	2	39
8	29	1	10	+	17	43	38	13
42	23	30	26	20	3	19	40	6
16	33	9	37	7	27	22	32	18

FIG. 8. Illustration of a trial sequence of the Letter Localization task. The letters on the stimulus card have been enlarged for illustration purposes.

continuous frame of reference. In addition, the fixation card remained illuminated for 500 ms after presentation of the letters to eliminate masking effects of the response grid. The response card was also presented at a slightly reduced illumination and remained visible until the subject responded.

Sixteen capital letters were used to construct 25 different letter pairs. Each letter was positioned so that its appearance would correspond with the centre of one of the numbered boxes on the response grid. Only the 30 boxes located in the three outermost columns on each side of the response grid were used, but subjects were unaware of this constraint. On a given trial, both letters always appeared in the same visual field. For each pair of letters presented in one field the same letters were presented, on a different trial, in the homologous positions in the opposite field. For example, the corresponding RVF stimulus for the trial depicted in fig. 8 was K-19, T-39. Of the 50 letters (25 pairs) 20 appeared above the horizontal midline, 20 below, and 10 on the horizontal midline in each field. Five additional stimulus cards were presented with letters positioned on or immediately adjacent to the vertical visual midline. These trials were included to determine if subjects were maintaining fixation and were not used in the analysis of visual field performance. Subjects were instructed to report verbally both the name and the exact location of each letter and were encouraged to guess if they were unsure about either judgement. Subjects received 10 practice trials to familiarize them with the procedure, followed by 105 experimental trials.



Correct response.
'Snow 3'

FIG 9. Illustration of a trial sequence of the Word Orientation task. The word on the stimulus card has been enlarged for illustration purposes.

Experiment 7: word orientation. This experiment was run approximately two years after the other visual hemifield studies. A new group of 6 right-handed males, similar to G.B. in age and education, served as controls. The general procedure was the same as employed for Letter Localization (*see* fig. 9): 48 four-letter, high frequency nouns served as stimuli (frequency 55 per million; Carroll *et al.*, 1971). Each word was presented once in each visual field at the same orientation. All words were written in capital letters with the individual letters positioned in their normal orientation. Each word was positioned so that the space between the second and third letter fell on the horizontal midline, 2 deg 46 min from fixation. The maximum visual angle subtended by the words was 2 deg 32 min in the horizontal and vertical plane (orientations 1 and 5 respectively, *see* fig. 9). On each trial the subject was required to report both the word and its orientation verbally by referring to the numbered lines on the response card.

It should be noted that the orientation template was located in the centre of the response card so that the exact location of the letters could not be used as an aid for determining orientation. Testing began with 10 practice trials followed by 96 experimental trials.

Results and Discussion

Letter localization. G.B., as well as normal subjects, produced near perfect levels of accuracy for naming and localizing letters presented along the visual vertical midline suggesting that good fixation was maintained throughout testing. Accuracy for letter identification and exact localizations in the lateral fields is presented in fig. 10. The results from the normal subjects were submitted to an analysis of variance with repeated measures on the Visual Field and Judgement Factors. This analysis revealed a significant main effect for Judgement (F(1,5) = 29.0, $P < 0.01$) with every subject being more accurate at localizing than naming for both LVF and RVF presentations. There was also a significant interaction of Visual Field and Judgement (F(1,5) = 7.3, $P < 0.05$) due to a slight RVF advantage for letter naming concurrent with a LVF advantage for specifying their location (*see* fig. 10).

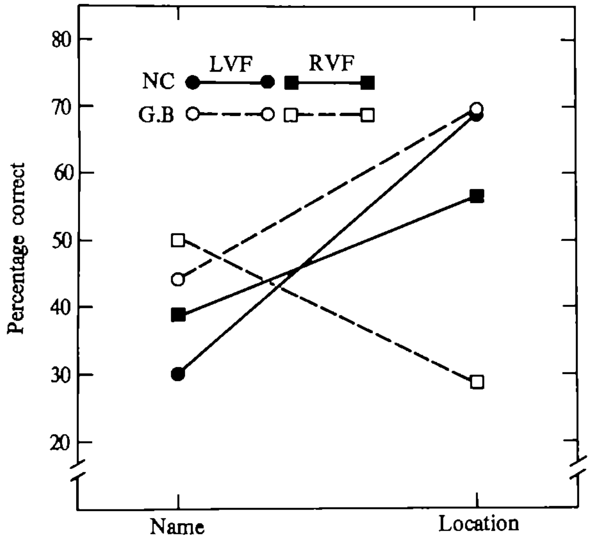


FIG. 10. Mean percentage of correctly named letters and correct localizations in the LVF and RVF by normal control subjects (NC) and G.B.

The acallosal patient performed within the normal range in both the LVF and RVF for letter naming (Z = +0.68 and +0.55 for the LVF and RVF, respectively), and tended to be more accurate at naming letters in the RVF relative to LVF presentations. For localization accuracy, G.B. again performed within the normal range on LVF presentations (Z = +0.14) and, like normal individuals, was more accurate at determining location than identity. In marked contrast, his ability to localize letters in the RVF was below the normal range, and more importantly, was actually poorer than his ability to name these letters. The discrepancy between these judgements was highly significant for RVF presentations (Zdz = 3.14, $P < 0.001$) but not for LVF presentations (Zdz = 0.59).

The difference in performance between G.B. and normal subjects may be more clearly appreciated by referring to fig. 11. Responses to each letter were scored according to the four possible response combinations. Note that for LVF presentations G.B.'s pattern of responses was similar to normals, with a greater percentage of responses which were correct for location but incorrect for name than

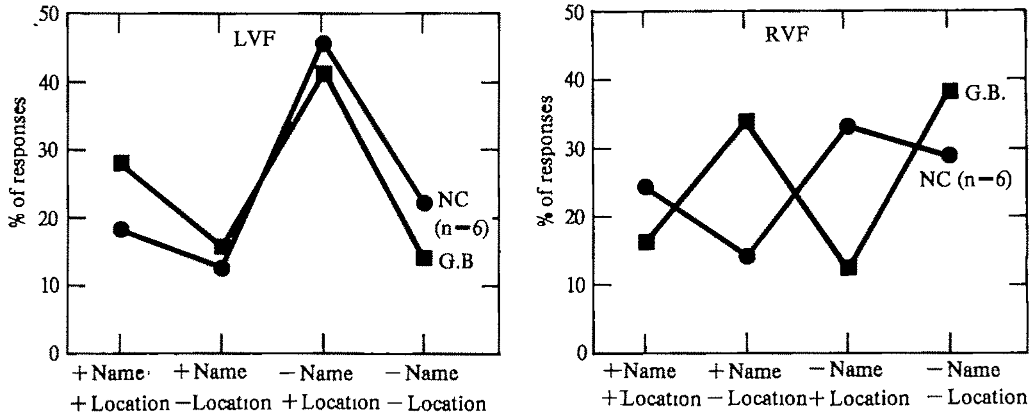


FIG. 11. Pattern of response choices by normal control subjects (NC) and G B. on the Letter Localization task.

responses which were correct for name but incorrect for location. For RVF presentations normals preserved this relationship. G.B., however, produced a reverse pattern, and in fact correctly named, but incorrectly specified the location of approximately 35 per cent of the letters presented in the RVF.

Word orientation. The pattern of results was highly similar to the findings on the Letter Localization task. An analysis of variance of the normal subject's scores revealed a significant main effect for the Judgement Factor due to a consistent superiority for specifying orientation relative to word reading ($F(1,5) = 72.1$, $P < 0.001$), and a significant interaction of Visual Field and Judgement resulting

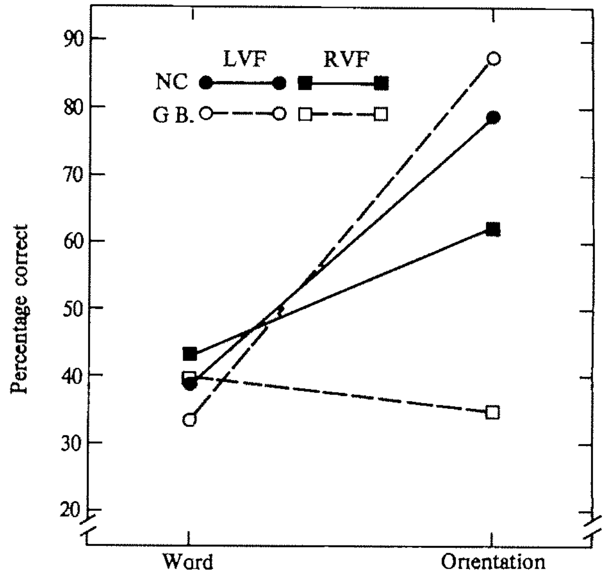


FIG. 12. Mean percentage of correctly read words and judgements of orientation in the LVF and RVF by normal control subjects (NC) and G.B.

from a RVF advantage for reading words concurrent with a LVF advantage for indicating their orientation ($F(1,5) = 27.3$, $P < 0.01$) (*see* fig. 12).

The acallosal subject was again found not to differ from normals when required to read words. This was true with respect to overall level of accuracy ($Z = -0.42$ and $Z = -0.23$ for the LVF and RVF, respectively), and RVF advantage. For judgements of orientation, however, he scored within the normal range when words appeared in the LVF ($Z = +0.98$) but was significantly worse than normal subjects in the RVF ($Z = -2.68$, $P < 0.01$). As a result, the discrepancy between visual fields was significantly greater than normal for judgements of orientation ($Zdz = 3.52$, $P < 0.001$); but not for word reading accuracy ($Zdz = 0.85$). Finally, within the RVF alone the discrepancy between reading a word and specifying its orientation was significantly greater than expected ($Zdz = 3.88$, $P < 0.001$).

In light of G.B.'s poor performance for localizing and specifying the orientation of the material presented in the RVF, an attempt was made to determine if his errors were qualitatively different as well. Inspection of the responses, however, failed to support this possibility. On the Letter Localization task the majority of errors committed by normal subjects were misplacements which were usually one, and rarely more than two boxes away from the actual stimulus location. The acallosal subject produced similar errors for both LVF and RVF presentations. Misplacements in the RVF were simply more frequent and tended to include a higher proportion of greater than two box mislocalizations. There was, however, no apparent tendency to misplace stimuli in a particular direction or a greater difficulty in the upper *versus* the lower quadrant of the RVF.

On the Word Orientation task the majority of orientation errors produced by normal subjects were committed, as would be expected, on words orientated at oblique angles. Horizontal and vertical orientations were rarely misjudged. Similarly, for RVF presentations G.B. correctly specified the orientation of 5 of the 6 words written horizontally and 4 of the 6 presented vertically, while misjudging all words at orientations 3 and 6, and all but one word at orientations 4 and 7 (*see* fig. 9). Thus, G.B.'s ability to judge the location and orientation of RVF stimuli appeared to be quantitatively poorer, but not qualitatively different, than normal.

These results support the findings of the previous studies which suggested a dissociation between stimulus identification and localization with material initially presented to the left hemisphere, and extended this finding to the perception of orientation. Since both an identity and a spatial judgement were required for each presentation, the possibility that the pattern of results on the previous studies was due to procedural differences was eliminated. In addition, the possibility that the patient's difficulty with RVF presentations may have resulted from a generalized attentional deficit, or a limited allocation of resources, may also be rejected since he performed at normal levels on the more difficult task of stimulus identification while being impaired on the relatively easier judgements of location and orientation. Thus, the difficulty experienced by the acallosal subject appeared to be directly related to the type of processing required.

GENERAL DISCUSSION

Across several different tasks and procedures a consistent pattern of results emerged. Specifically, the acallosal subject exhibited a selective impairment of spatial processes when material was initially presented to the left hemisphere, concurrent with normal ability to identify and recognize material verbally in both the LVF and RVF. Before discussing the possible relation between this pattern of findings and the absence of the corpus callosum, an alternative explanation, namely the presence of a unilateral lesion, must be addressed since the observed deficit was clearly limited to the RVF.

While the possibility of an extracallosal lesion cannot, of course, be completely excluded, this alternative may be questioned on both structural and behavioural grounds. Specifically, the CT scan failed to reveal any cortical damage and there was no behavioural evidence suggestive of left posterior dysfunction (e.g. language deficits, constructional apraxia, astereognosis, graphaesthesia, or finger agnosia on either hand, or any apparent visual perceptual deficits with stimuli in free field). Alternatively, it may be argued that, since certain subcortical structures have been implicated in spatial functions (Schneider, 1967; Trevarthen, 1968), G.B.'s deficit may be attributed to, for example, a lesion of the left superior colliculus and/or its connections to the posterior parietal lobe *via* the pulvinar. In fact the patient's presenting symptoms (hypothermia and episodic hyperhidrosis) did suggest dysfunction of midline subcortical structures (most probably the arcuate nuclei of the hypothalamus; Noël *et al.*, 1973) and therefore may be interpreted as being consistent with the possibility of other subcortical abnormalities. However, even if such a lesion were present, it is doubtful that it would have produced the present findings since, even in nonhuman primates, large lesions of the superior colliculus reportedly effect detection and localization only when stimuli are presented in the extreme periphery (i.e., 40 deg or more from fixation; Butter *et al.*, 1978). Since in the present experiments all presentations were within 4 deg of fixation it is unlikely that the tectal system would play a critical role, especially in making the fine localization and orientation judgements that were required on these tasks.

The remaining possibility is that the RVF spatial impairment was a direct consequence of the absence of the corpus callosum. However, since the patient's normal ability to verbalize LVF material strongly suggested that interhemispheric transfer could occur, the question remains as to why this capability did not also extend to spatial information.

Ultimately, an explanation for this qualitative limitation will require specification of the systems subserving normal recognition and spatial abilities both in the left and right hemispheres and the pathways (cortical and subcortical) supporting their interaction. Nevertheless it is likely that, as reviewed in the Introduction, interhemispheric transfer is mediated by the anterior commissure in cases of callosal agenesis, especially when complex information is involved. If so, then use of this pathway would require that information initially received at the striate cortex be transmitted anteriorly into the temporal lobe before transfer.

Anatomical investigation has revealed the presence of such a fibre tract (the inferior longitudinal fasciculus), which emanates from the prestriate cortex and continues along the inferior temporal gyrus. In addition, lesions of this inferior temporal region have been found selectively to disrupt visual recognition, but not spatial functions, in the monkey (*see* Ungerleider and Mishkin, 1982, for review). Studies of human subjects have also revealed visual recognition deficits following temporal lobe damage (e.g. unilateral temporal lobectomy), right temporal removal producing greater impairment than left resection (*see* Kimura, 1963; Meier and French, 1965; Lansdell, 1968; Milner, 1968). Moreover, this recognition deficit may be doubly dissociable from the spatial impairments produced by right parietal injury (Newcombe and Russell, 1969).

In support of this behavioural specificity electrophysiological studies have indicated that a majority of inferior temporal neurons are particularly responsive to complex visual stimuli and relatively insensitive to changes in their position and orientation (Gross *et al.*, 1972, 1977). Furthermore, this insensitivity to spatial manipulation may be viewed as a necessary consequence of the fact that many of these neurons have large bilateral receptive fields, receiving information from the contralateral field *via* cortical connections within the same hemisphere, and information from the ipsilateral field transferred from the opposite hemisphere *via* both the corpus callosum and anterior commissure (Rocha-Miranda *et al.*, 1975; Gross *et al.*, 1977). It has been suggested that this bilateral convergence of information may underlie, in part, the specialized role of the temporal lobe in identifying and recognizing visual stimuli independent of their location or orientation (Gross and Mishkin, 1977). This property, however, would render this area particularly ill-suited for the encoding and transmission of spatial information, especially to the extent that such processing is dependent on the maintenance of a retinotopic organization. As a result, transfer *via* the anterior commissure would be limited to nonspatially organized information. Therefore, for the acallosal subject the discrepancy between the left and right hemispheres on spatial tasks may be a reflection of the inferior ability of the left posterior region to perform such analyses when disconnected from the right. It is assumed that verbalization of the spatial analyses performed by the right hemisphere is possible since all that must be transferred in this case is the result of these analyses, not the spatial information itself.

Two major implications follow from this analysis. (1) In the absence of the corpus callosum the anterior commisure may be capable of mediating transfer of information to be identified, but is incapable of transferring information for spatial analysis. Thus, interhemispheric transfer of such information may be limited to the corpus callosum. (2) If the difference between G.B. and normal individuals on spatial tasks is directly attributable to a lack of posterior hemisphere interaction, then the right hemisphere may normally participate in these functions, regardless of field of presentation. This would suggest that a patient with right parietal damage with neglect or inattention to the LVF should also show abnormally poor spatial abilities for material presented in the RVF. In contrast, left parietal damage should produce only a unilateral deficit (*cf.* Chédru *et al.*, 1973; Mesulam, 1981).

It is suggested that our understanding of interhemispheric communication may be further advanced by a more detailed examination of the discrepancies between the unilateral processing capabilities of acallosal subjects and normal individuals. It remains to be seen whether similar results would be found in other acallosal patients. The interpretation of the findings in all cases will ultimately require post-mortem confirmation that the corpus callosum was completely absent and that no other noncallosal lesions were present.

ACKNOWLEDGEMENTS

A portion of this report was presented at the Ninth Annual Meeting of the International Neuropsychological Society, February 4–7, 1981 in Atlanta, GA. The author wishes to thank Dr M. Mishkin for his valuable suggestions and encouragement throughout the course of these studies, Drs N. Geschwind, L. Costa and P Brouwers for their helpful comments on an earlier draft of this manuscript, Dr C. Clark for statistical consultation, and Dr P. LeWitt for providing the results of the neurological examination and allowing study of his patient. Special thanks are due to Dr P. Fedio for providing the facilities and time necessary to pursue this project.

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(*Received August 9, 1983. Revised June 26, 1984. Accepted July 24, 1984*)

Brain (1985), **108**, 65-80

LONG-LOOP REFLEXES IN SMALL HAND MUSCLES STUDIED IN NORMAL SUBJECTS AND IN PATIENTS WITH HUNTINGTON'S DISEASE

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SUMMARY

Long-latency electromyographic (EMG) responses of the first dorsal interosseus muscle were evoked by short displacements of the index finger in healthy subjects and in patients with Huntington's disease (HD). In all 20 healthy subjects the early spinal response (mean latency 31.5 ms) was followed by a reproducible later reflex response with a mean latency of 56.5 ms. The activity pattern of single motor units of the stretched muscle was similar to that of the surface EMG. Thus all single motor units tested could be active during either the first or second response phase, but never in both in a given trial. Of the 50 patients with HD, the late EMG response was missing completely in all but 7, but the early spinal component was almost identical to that of the control group. Double stretches at an interval of 25 ms evoked two similar EMG responses in these patients, proving that the motoneuron pool is still excitable during the time at which the second response would have appeared in healthy subjects.

The reflex responses of the thenar muscles evoked by electrical stimulation of the median nerve were examined during a voluntary opposing contraction of the thumb in both groups of subjects. In normal subjects, two EMG responses could be distinguished with latencies similar to those of the mechanically elicited responses. Patients with HD again lacked the second response, although the first spinal response was always present. The results are discussed with respect to different proposals concerning the origin of long-latency responses in human muscles. At least for distal hand muscles, the results suggest that the long-latency responses are long-loop reflexes.

INTRODUCTION

The original concept of a transcortical reflex transmitting proprioceptive information back to the muscle of origin (Phillips, 1969; Evarts, 1973) has recently been supported by recordings from pyramidal tract neurons in monkeys. Cheney and Fetz (1984) were the first to show that corticospinal neurons exhibited short-latency responses to the stretching of muscles to which these cells projected *via* an oligosynaptic pathway.

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In man, it is more difficult to prove the existence of such an oligosynaptic transcortical loop. The averaged electromyographic (EMG) response of arm muscles to load changes does indeed show components at latencies compatible with a supraspinal or even transcortical reflex pathway. The existence of such a route is further supported by the absence of the late EMG responses in patients with defined supraspinal lesions (Lee and Tatton, 1975; Marsden *et al.*, 1977*b*, 1978) and by the occurrence of pathologically enhanced long-latency components in patients with cortical reflex myoclonus, a condition characterized by enhanced amplitudes of the early cortical somatosensory evoked potentials (Halliday, 1967; Sauer and Schenck, 1977; Hallett *et al.*, 1979). Nevertheless, recent results throw doubt on the validity of long-latency EMG responses as an indicator of supraspinal reflex transmission. Long-latency EMG responses can be obtained in spinal animals (Ghez and Shinoda, 1978; Tracey *et al.*, 1980) and may be due to repetitive bursts of primary muscle spindle endings signalling small oscillations of the stretched muscles (Hagbarth *et al.*, 1980, 1981). Another conceivable hypothesis attributes the second EMG response to the excitation of motoneurons *via* secondary muscle spindle afferents (Matthews, 1983, 1984).

Despite such objections, there is no reason to believe that the transcortical reflex contributing to motor performance in monkeys should have lost its significance in man with his even more highly developed corticospinal control. Furthermore, all the arguments in favour of a peripheral or spinal origin of the late EMG responses do not rule out a transcortical reflex path, but merely call for experiments in man in which these facultative sources can be excluded. In this report, small transient displacements of the index finger were used to evoke long-latency reflexes in an intrinsic hand muscle, the first dorsal interosseus muscle. This muscle was chosen because it is known that the corticospinal tract strongly projects to distal hand muscles (for review *see* Phillips and Porter, 1977). The results obtained in normal subjects and in patients with Huntington's chorea, a degenerative disease with markedly reduced somatosensory evoked cortical potentials (Oepen *et al.*, 1981; Josiassen *et al.*, 1982; Noth *et al.*, 1984*a*), strongly support the view that, at least in distal hand muscles, long-latency reflexes can be attributed to a supraspinal pathway. A brief account of the results has been published elsewhere (Noth *et al.*, 1983).

METHODS

General Procedure

While most of the earlier work on long-latency reflexes has been done on more proximal arm muscles, an intrinsic hand muscle—the first dorsal interosseus muscle—was the object of the present study. The motor paradigm resembled the precision grip, which in most instances is executed under isometric conditions (Napier, 1956). Subjects were asked to exert a steady flexing force by pressing the middle joint of the index finger against a slider fixed to a lever. The counterpart of this flexing force was an opposing force of the thumb against a rigid support. The isometric force exerted by the subject was displayed on an oscilloscope screen for visual control. A target beam on the same screen indicated the desired force, which in most instances was 10 per cent of the maximum voluntary force. During the isometric holding task, an electromagnetic vibrator connected to the lever delivered short transient dorsiflexions of the index finger (1.2 deg, measured at the proximal finger joint). The imposed movement lasted 20 ms, with a time to peak of about 6 ms. The excursions were generated at pseudorandom intervals (shortest interval 400 ms, mean 1.5 s). In some experiments, double stretches were applied at an interval of 25 ms between onsets. In general, two runs consisting of 64 to 128 stretches were carried out on either hand.

Mechanical Stretching Device

The principal component of the stretching device was an electromagnetic vibrator (Ling Dynamics System), controlled by a position and velocity feedback system which has been described in detail in a previous publication (Noth *et al.*, 1984*b*). The moving shaft of the vibrator was connected to a lever by a joint-coupling. The linear movement of the shaft resulted in a rotation of the lever about a vertical axis. The length of the lever was 130 mm and the compliance was 1.5×10^{-5} rad/Nm, measured for a torque applied to the lever under static conditions. The system thus behaved isometrically.

EMG Recordings and Analysis

The EMG activity of the first dorsal interosseus muscle was recorded with surface electrodes, one placed over the belly of the muscle, the other over the dorsal aspect of the proximal phalanx of the thumb. The EMG signal was filtered (corner frequencies 5 and 1000 Hz), rectified and averaged over 64 to 128 trials (Tönnies signal averager), using the onset of stretch as the trigger point. Analysis time was 200 ms, with a sampling rate of 5120 points/s (1024 bins). Latency and duration of the reflex responses to imposed displacements of the index finger were determined by visual inspection of the EMG records on the oscilloscope by means of a cursor. Responses were quantified using a desktop computer for digital processing (Apple II). To obtain information about the typical time course of the EMG responses of different subpopulations, averaged EMG curves were constructed with a sampling interval of 4 ms and plotted with standard deviations (fig. 4).

In 3 healthy subjects the response of 27 single motor units of the first dorsal interosseus muscle to the imposed stretches was studied using small concentric needle electrodes. The motor unit potential was fed into a spike discriminator and converted into a square pulse (width 2 ms). The discriminator pulse was then averaged (500–1000 trials) at a fast sampling rate (bin width 0.2 ms) to achieve a high time resolution. For 8 units a conventional poststimulus time histogram was constructed off-line (bin width 2 ms) and compared with the averaged response obtained on-line. The corresponding patterns looked similar in all respects. In this particular experiment the subjects were asked to hold the firing level of the selected motor unit steady (around 10 Hz in all units tested). Control of the firing rate was aided by acoustic feedback by means of a loudspeaker. Thus the flexing force varied among the test runs.

Reflexes in Thenar Muscles Evoked by Median Nerve Stimulation

The method chosen has been described in detail by Conrad and Aschoff (1977). Two surface recording electrodes were positioned over the ball of the thumb and midway along the proximal phalanx of the thumb. For stimulation of the median nerve, surface electrodes were positioned longitudinally over the nerve at the wrist with the cathode proximal to the anode (stimulus duration 0.2 ms, rate 1/s, constant current source). Stimulus intensity was chosen to be either just subthreshold or well above the threshold for motor fibres of the median nerve, as judged by the EMG response and the contraction of the thenar muscles. The subjects were instructed to press the distal phalanx of the thumb against a piezo-element under isometric conditions. The contractile force, which was displayed on an oscilloscope screen for visual control, was 50 per cent of the maximal voluntary force during the test period. The force level was chosen so that clear reflex responses could be elicited, as Upton *et al.* (1971) have already shown that the amplitude of the reflex components is generally larger as the contractions become more intense. The averaging procedure was identical to that described above for mechanical stimuli. Both right and left hands were examined and each measurement was repeated at least once. Latency and duration of the EMG responses, which were first described by Upton *et al.* (1971), were determined by visual inspection of the EMG records.

Subjects

Twenty normal subjects participated in the present study, 10 females and 10 males, aged 17 to 75 years (mean 34 years). The group of patients consisted of 50 persons with clinically manifest Huntington's disease (HD). Diagnosis was based on a definite familial history (autosomal dominant) and on the characteristic hyperkinetic movements (for recent review, *see* Hayden, 1981). The age of the 25 females and 25 males ranged from 21 to 69 years (mean 42 years). The mean time from the onset of neurological symptoms was 7 years, ranging from less than 1 year to 17 years. Patients with advanced hyperkinetic movements were excluded. Twenty-seven patients were unmedicated at the time of the study; 13 received tiapride (300–600 mg/day) for a mean duration of eight months. Other neuropharmacological agents have only been prescribed to single patients and will not be mentioned in detail.

Informed consent was obtained from all patients and control subjects participating in the study.

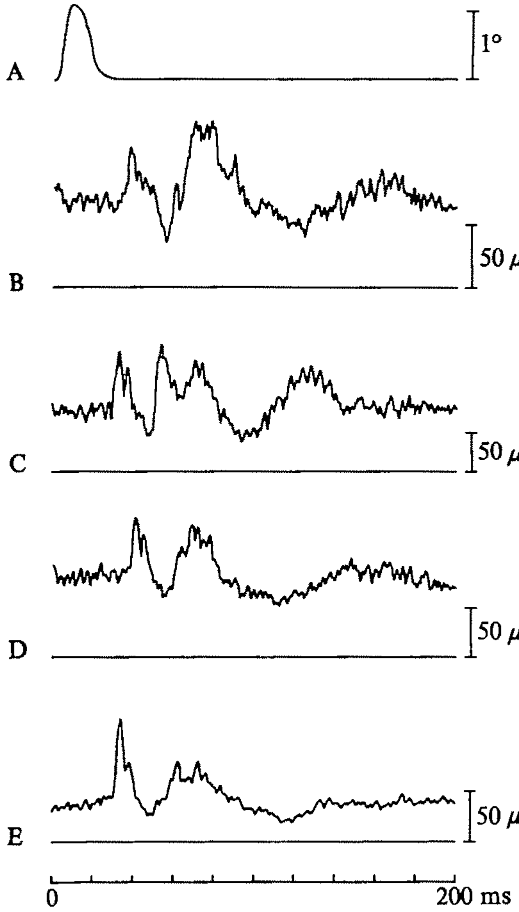

FIG. 1. Representative EMG responses of the first dorsal interosseus muscle to imposed finger displacement in 4 healthy subjects. A, angular displacement of the lever, corresponding to a similar displacement of the index finger at the metacarpophalangeal joint (single trace). B–E, surface EMG of first dorsal interosseus muscle (rectified and averaged over 64 to 128 trials). Subjects aged 55, 31, 28 and 19 years (from above down).

RESULTS

Stretch Responses

In all normal subjects the imposed finger displacements evoked two clearly separable EMG responses of the stretched first dorsal interosseus muscle. In fig. 1, four representative examples are shown. The first increase in EMG activity reflects the monosynaptic segmental reflex with a mean latency to onset of 31.5 ± 2.6 ms (mean ± SD, n = 20) and a mean duration of 15.2 ± 2.5 ms. In a number of records the first response comprised two peaks separated by only 6 to 8 ms, due to the fact that in these cases a sharply synchronized biphasic wave was present in the nonrectified averages (not shown).

The late response had a mean latency to onset of 56.5 ± 4.3 ms and a mean duration of 27.7 ± 7.0 ms. In most of the subjects no consistent segmentation of the second response could be discerned. In 7 of the 20 subjects, a reproducible third increase in EMG activity occurred with a latency of about 67 ms (fig. 2).

The voluntary reaction time to the kinaesthetic stimulus was determined in 6 subjects. The subjects were instructed to flex the index finger as quickly as possible in response to the stimulus, and the resultant EMG pattern was compared with the pattern obtained during the standard session. The deviation from the control curves began 70 to 90 ms after onset of stretch and was thus always later than the peak of the second EMG response.

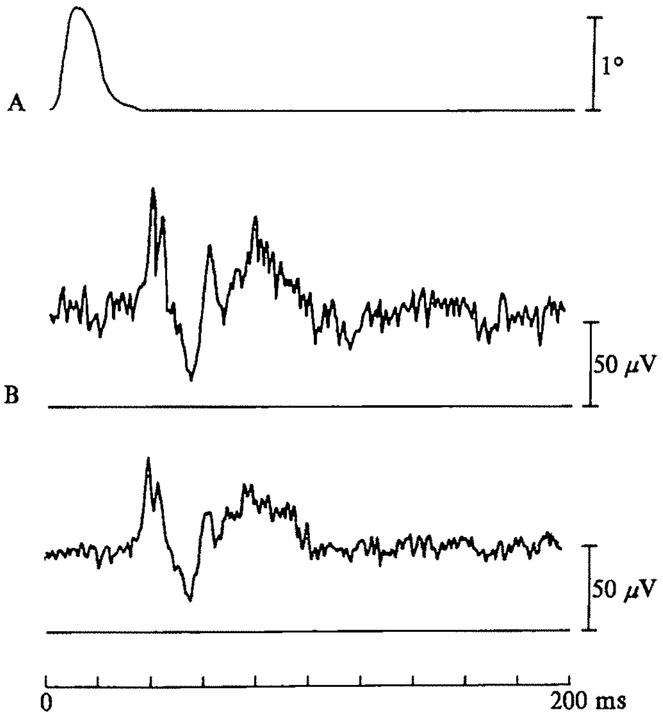

FIG. 2. EMG records from a healthy subject (aged 26 years) exhibiting a reproducible segmentation of the long latency response. A, angular displacement of index finger (single trace). B, surface EMG of first dorsal interosseus muscle, two consecutive runs (averaged over 128 trials each).

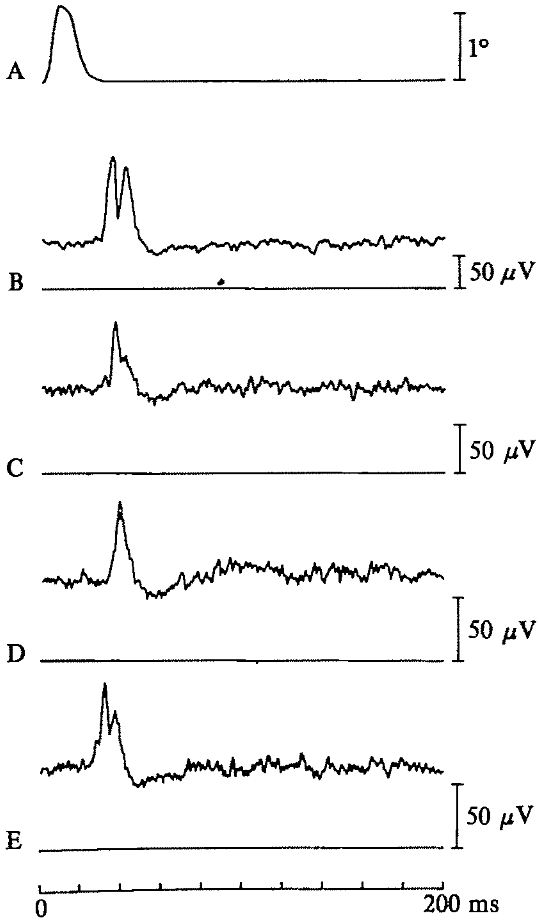

FIG. 3. EMG responses of first dorsal interosseus muscle to imposed finger displacements in 4 patients with HD; otherwise identical to fig. 1. Subjects aged 46, 52, 49 and 63 years (from above down).

Fifty patients suffering from HD were investigated. In these patients, the amplitude of the cortical somatosensory evoked potentials is drastically reduced (Oepen *et al.*, 1981; Josiassen *et al.*, 1982; Noth *et al.*, 1984*a*), indicating a diminished afferent inflow to the cortex. This leads to the question as to whether the long latency reflexes are reduced in these patients. Fig. 3 depicts four representative EMG records. In 32 of these patients, the late EMG component was completely lacking on both sides. In 11 patients, the late response was absent only on one side, and in 7 patients a second EMG response was preserved on both sides. The spinal reflex component, on the other hand, was identical with that of the control group, as can be seen in fig. 4, in which the grand averages over both groups are depicted.

To explore whether in patients lacking the late EMG response a second afferent volley is capable of exciting alpha motoneurons at the same time at which the late EMG response appears in healthy subjects, double stretches were applied at an

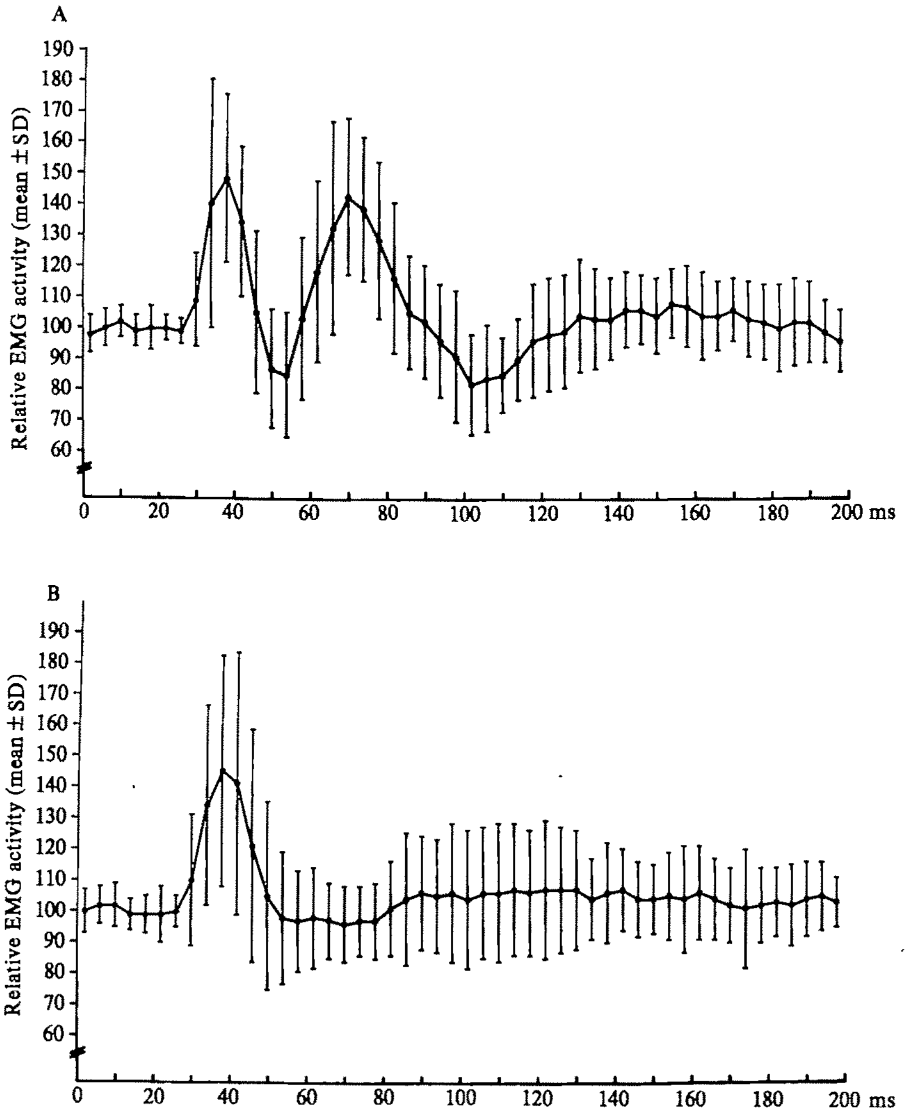

Fig. 4. EMG response of first dorsal interosseus muscle to imposed finger displacements. Grand averages (mean ± SD) of the EMG records of 20 normal subjects (A) and of 50 patients with HD (B), all recordings from right hand. EMG magnitude is expressed as percentage of the mean EMG activity during the first 20 ms following onset of stretch, sampling width 4 ms. Mean age of healthy subjects 34 years, that of the patients 42 years.

interval of 25 ms. This interval was chosen because it is roughly the mean latency between the first and the second EMG responses in the healthy group. All 16 patients tested responded with two distinct EMG peaks to the double stretches (fig. 5).

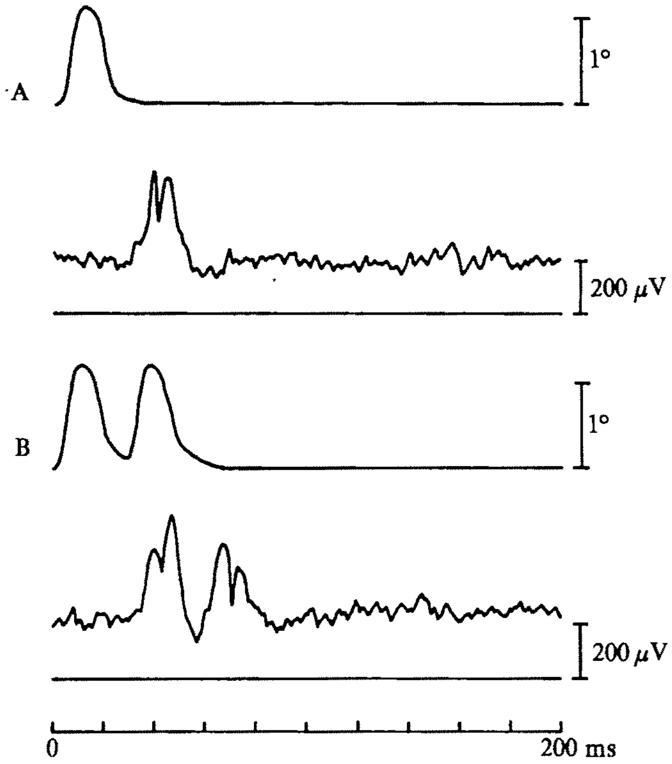

FIG. 5. EMG response of first dorsal interosseus muscle to single stretch (A) and double stretch (B) in a patient with HD (aged 42 years). *Upper traces.* angular displacement of index finger (single trace). *Lower traces.* surface EMG of first dorsal interosseus muscle (64 rectified and averaged trials).

In 3 healthy subjects the firing pattern of 27 motor units of the first dorsal interosseus muscle was studied to ascertain whether units were preferentially active during one or the other of the two EMG responses, as has been described by Bawa and Tatton (1979). Another aim was to obtain information about the exact timing of single units during the test run. Fig. 6 shows a typical single unit response. As in this case, no unit was found which was active only during one EMG response phase, although a slight preference for the first or second response could be observed in 3 units. In no case did a given unit discharge during both the first and the second EMG response in the same sweep of 200 ms; this ruled out synchronization of alpha motoneurons due to enhanced probability of firing after the segmental reflex as the cause of the second EMG peak. The mean time interval between the onset of the two responses was 28.7 ± 4.6 ms in the 24 units exhibiting both responses, which compares well with the value of 28.2 ± 3.1 ms obtained in the surface EMG recordings. Again, a few units (3 of 27) showed a consistent third increase in activity, following the second response by about 15 ms. The simultaneously recorded surface EMG revealed a similar pattern in these cases.

Long-latency Responses Evoked by Median Nerve Stimulation

It is well known that electrical shocks applied to a mixed nerve can generate two electromyographic reflexes in the muscles supplied by that nerve (Upton *et al.*, 1971;

Milner-Brown *et al.*, 1975; Conrad and Aschoff, 1977; Stanley, 1978). In the thenar muscle, the latency of the second excitatory response is about 50 ms and thus equals that of the mechanically evoked response. The stimulus intensity necessary to elicit such a late EMG response lies below the threshold for the motor fibres (Stanley, 1978), as demonstrated in fig. 7A for a normal subject. It can therefore be assumed that the receptor responsible for the second EMG response belongs to the group I afferents, so that flexor reflex afferents cannot be responsible for this type of long-latency reflex. Grouped afferent discharges as a source of long-latency EMG responses (Hagbarth *et al.*, 1981) can also be discarded, because there is no change in the mechanical state of the muscle when low stimulus intensities are used. If it is true that the late electrically evoked EMG response is due to a supraspinal reflex, as has been suggested by several authors (Milner-Brown *et al.*, 1975; Conrad and Aschoff, 1977; Iles, 1977; Chofflon *et al.*, 1982), the electrically evoked response would be expected to be missing in patients lacking the long-latency stretch response.

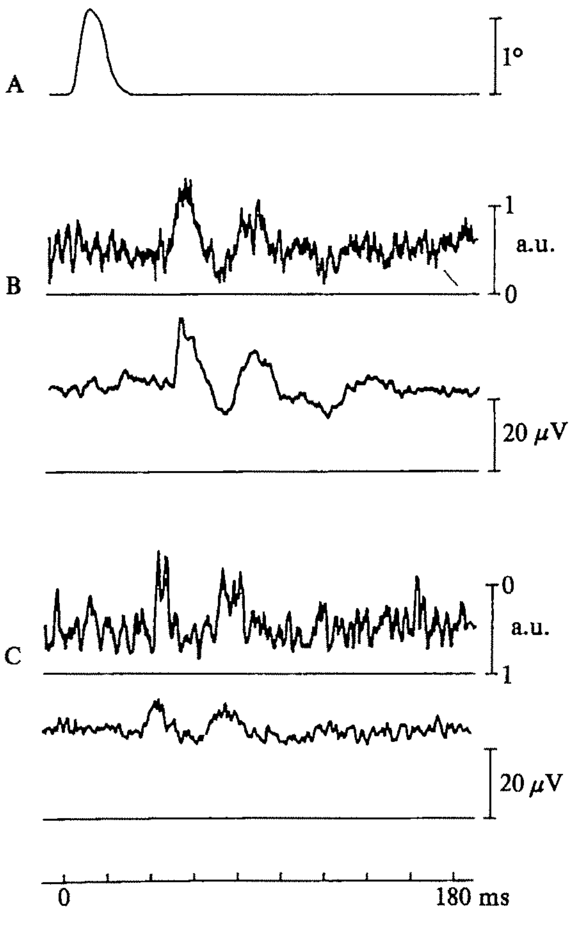

FIG. 6. Surface EMG response and single motor unit response to imposed finger displacements in a healthy subject aged 40 years. A, angular displacement of index finger (single trace). B, motor unit recruited at 5 per cent maximal force, 1024 trials averaged. C, motor unit recruited at 2 per cent maximal force, 256 trials averaged. Upper traces of B and C: motor unit response. Lower traces of B and C simultaneously recorded surface EMG. a.u. = arbitrary units.

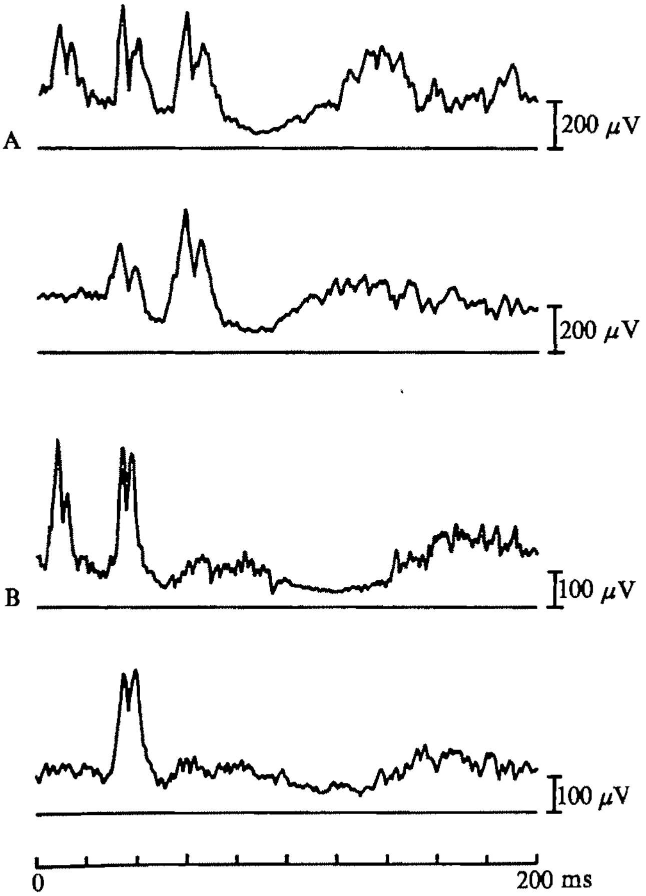

FIG. 7. EMG response of thenar muscles to electrical stimulation (single shock) of the median nerve during an isometric voluntary contraction of about 50 per cent maximum force. Surface EMG records (rectified and averaged over 32 trials) for a healthy subject aged 39 years (A) and a patient with HD aged 45 years (B). Stimulus applied at onset of sweep. *Upper traces* of A and B: stimulus intensity just suprathreshold for motor nerve fibres. *Lower traces*: stimulus intensity subthreshold for motor nerve fibres.

Ten healthy subjects served as a control group. The mean latency of the first, segmental response was 29.7 ± 1.8 ms, and its mean duration 12.2 ± 2.0 ms. The second response (mean latency 52.0 ± 3.7 ms, mean duration 17.7 ± 5.5 ms) was clearly visible in all normal subjects. Ten unselected patients with HD were investigated, all of whom lacked the electrically evoked late response; latency (29.3 ± 2.7 ms) and duration (12.6 ± 2.1 ms) of the first response, which was present in all patients, were similar to that of the control group. Even raising the stimulus intensity well above the motor threshold produced no late EMG response. A typical example is given in fig. 7B.

DISCUSSION

A primary aim of this study was to elaborate a perturbation paradigm by which reproducible long-latency EMG responses could be elicited in distal hand muscles, and to explore whether these responses are transmitted *via* a supraspinal pathway.

The discussion to follow will therefore focus on the question of whether the data presented are sufficient evidence to allocate the second EMG response to a supraspinal pathway.

Resonance Hypothesis

According to a recent experimental study, segmented EMG activity may be the consequence of mechanical oscillation of the stretched muscle, sensed by the primary muscle spindle endings (Hagbarth *et al.*, 1981). A strong argument against segmented Ia input being responsible for the second EMG response in the present paradigm is the lack of such a peak in HD patients. The fact that a second afferent volley generated by the double stretch provokes a second EMG response of appreciable size in HD patients has two implications. First, it proves that a second incoming volley is quite capable of exciting the motoneuron pool at the same time as the second response occurs in healthy subjects. An increase in Renshaw inhibition or any other change in the excitability of alpha motoneurons in HD patients is therefore unlikely to be responsible for the absence of the long-latency reflex. Secondly, the response to double stretches suggests that the small triangular pulse used in the present study failed to generate a second Ia volley of sufficient strength to excite the alpha-motoneurons a second time after the monosynaptic response. There is no reason to assume that in HD patients muscle mechanics or the sensitivity of the primary spindle endings differ from those in healthy subjects, a view which is supported by the equal size of the monosynaptic response in the two groups. In line with this assumption is the observation that similar short-lasting stretches have been used in cat soleus muscle to study the synaptic effects of pure Ia volleys, and no grouped inflow has been reported to occur (Stuart *et al.*, 1970). This result was confirmed by microneurographic recordings in normal cats (Prochazka and Wand, 1981).

According to Lee and Tatton (1982), reducing the duration of the imposed displacement of the wrist reduces the size of the long-latency reflex in the stretched wrist flexors. A brief pulse of 40 ms even failed to evoke a second EMG response, while leaving the segmental response unaltered. This result is not in line with the findings presented here. It is possible that in distal hand muscles the gain of the supraspinal reflex pathway is larger than in more proximal muscles, where a greater amount of temporal facilitation might be needed to generate the second response. Another explanation is based on Hagbarth's resonance hypothesis (Hagbarth *et al.*, 1981). It is conceivable that small muscle oscillations induced by the torque pulse can only be sensed by the primary spindle afferents when they occur during an ongoing muscle stretch. This would mean that in proximal arm muscles, grouped Ia input would be at least partly responsible for the generation of long-latency responses when longer-lasting torque pulses are applied. Finally, a stronger postexcitatory depression of alpha-motoneurons supplying proximal rather than distal arm muscles should be considered. Such a depression following stretch-induced excitation may be inferred from the well-known H-reflex depression after a conditioning shock in proximal limb muscles (Magladery *et al.*, 1952). Further work is needed to clarify this issue.

Slowly Conducting Afferents

Delayed EMG responses may be generated by slowly conducting afferents such as secondary muscle spindle afferents (Matthews, 1984), which in the cat are known to excite their homonymous alpha motoneurons (Matthews, 1969; Kirkwood and Sears, 1974; Stauffer *et al.*, 1976). It can, however, be expected that all primary spindle afferents within a muscle nerve are excitatory to their homonymous alpha motoneurons (Mendell and Henneman, 1971; Sypert *et al.*, 1980). Thus a continuum of muscle spindle afferents from primaries to secondaries exists which excites the homonymous motoneuron pool. It therefore seems unlikely that the steeply rising second EMG peak (*cf.* fig. 1B and C) is generated by secondary spindle afferents.

Another argument against the hypothesis put forward by Matthews is based on the experiments with electrical nerve stimulation. Although it cannot be proved that the two kinds of long-latency responses (mechanically and electrically evoked) share a similar pathway, their equal delay of onset after the monosynaptic response and their absence in HD patients favour this assumption. Secondary spindle afferents are not then required to elicit the long-latency response, because the intensity of the electrical stimulus is well below the threshold of motor fibres and thus also below the threshold of secondary spindle afferents. The same argument would rule out flexor afferents other than secondary spindle afferents as the cause of the electrically evoked second EMG response. Nevertheless, a contribution of secondary spindle afferents to the stretch-evoked long-latency component cannot be entirely excluded on the basis of our results. It should be stressed, however, that the evidence that spindle secondary endings are responsible for the long-latency reflex in the flexor pollicis longus (Matthews, 1984) is valid only for a component at 40 ms. Vibration of the pad of the thumb elicits a consistent long-latency response at about 55 ms (Matthews, 1984, figs. 3, 6, 7), which corresponds well with the response described here, even taking into account a somewhat longer peripheral conduction delay to the first dorsal interosseus muscle (around 12 cm). Since vibration was used by Matthews to circumvent the excitatory action of ramp stretches on secondary spindle endings, the component at 55 ms cannot be attributed to this type of spindle ending.

Other Mechanisms

Stimulation of skin receptors can produce EMG patterns in distal hand muscles (Jenner and Stephens, 1979, 1982) similar to those seen with brief finger displacements. Experiments with finger anaesthesia support the notion that cutaneous receptors contribute to the mechanically evoked long-latency response (Marsden *et al.*, 1977*a*; Jenner and Stephens, 1979; Westling and Johansson, 1984). There is good reason to assume that a supraspinal pathway exists for cutaneously elicited long-latency reflexes (Jenner and Stephens, 1979; Lemon, 1981; Strick and Preston, 1982). It is thus likely that both receptor types contribute to the long-latency reflexes observed in response to rapid finger displacements, and no attempt has been made in the present study to distinguish between the contributions of cutaneous and deep receptors to the observed second EMG response.

Supraspinal Transmission

In the final analysis, a supraspinal origin of the second EMG response seems to be the most reasonable explanation for the results presented here. The arguments for and against a transcortical reflex loop *versus* other supraspinal loops have recently been reviewed (Wiesendanger and Miles, 1982) and will not be taken up here. It should, however, be stressed that the drastic diminution of the early somatosensory evoked cortical potentials in patients with HD (Oepen *et al.*, 1981; Josiassen *et al.*, 1982; Noth *et al.*, 1984*a*), who lack the second EMG component, strongly supports the view that a transcortical loop is involved.

The lack of long-loop reflexes in HD patients may thus be a direct consequence of the diminished somatosensory input to the cerebral cortex. This notion is supported by the fact that no pyramidal symptoms indicating a central efferent lesion were detectable in our sample of HD patients. These patients exhibit normal somatosensory evoked neck potentials recorded over the second cervical vertebra (Noth *et al.*, 1984*a*), which is indicative of undisturbed impulse transmission up to the dorsal column nuclei (Stöhr *et al.*, 1982). The interruption thus seems to be confined to the thalamus or the cortical projection areas. Degeneration of small neurons within the ventrobasal complex of the thalamus and within the postrolandic cortex has been described in HD (Dom *et al.*, 1976; Lange, 1981) and so far no attempt has been made to differentiate between these structures in relation to the site of the impaired transmission in the lemniscal pathway. Nevertheless, exclusive degeneration of small neurons does not favour an involvement of relay neurons within the thalamus or the cerebral cortex. Therefore an inhibitory mechanism should also be considered, similar to the inhibition of relay neurons in the dorsal column nuclei as demonstrated in the cat (Oscarsson *et al.*, 1966).

An attractive hypothesis relates to the behavioural aspect of the transcortical reflex loop. It may be speculated that in HD patients the dysfunction of the basal ganglia responsible for the choreiform movements also leads to a permanent inhibition of impulse transmission in the lemniscal system, at least as far as the input to areas 3a and 3b (according to Brodmann) is concerned, this being the most likely thalamocortical pathway involved in the transcortical reflex (for review *see* Wiesendanger and Miles, 1982). In functional terms this would mean that an open-loop motor command (ballistic movement) interrupts a closed-loop feedback system (transcortical reflex). Gating of early and middle range components of the cortical somatosensory evoked potentials during limb movements has been observed in man (Coquery, 1978; Rushton *et al.*, 1981; Angel *et al.*, 1984;

Grünewald *et al.*, 1984), but gating of the long-loop reflex during ballistic movements certainly needs to be confirmed or rejected by a more direct experimental approach.

ACKNOWLEDGEMENTS

We are grateful to Professors Karl-Erik Hagbarth, Mario Wiesendanger and Dr Sinclair Cleveland for valuable comments on the manuscript and to Dr Herwig W. Lange (Department of Psychiatry, University of Düsseldorf) for referral of the patients in his care. The work was supported by a grant of the Deutsche Forschungsgemeinschaft (SFB 200).

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(*Received April 24, 1984. Revised July 27, 1984. Accepted August 2, 1984*)

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FUNDAMENTAL IMPORTANCE OF ARTERIAL OXYGEN CONTENT IN THE REGULATION OF CEREBRAL BLOOD FLOW IN MAN

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SUMMARY

The relationships between cerebral blood flow (CBF), arterial oxygen content, whole blood viscosity and the transport of oxygen to the brain have been studied in 54 subjects with variations in arterial oxygen content resulting from alterations in haemoglobin concentration ranging from 5.7 to 19.1 g/dl. A highly significant relationship was found between CBF and arterial oxygen content, CBF altering to maintain the rate of transport of oxygen to the brain within certain limits. No significant effect of changes in blood viscosity was evident. In a multiple regression analysis arterial oxygen content emerged as the major determinant of CBF and after this effect had been taken into account there was no significant influence of blood viscosity, arterial pCO_2, age or mean arterial blood pressure. The results imply that the alterations in CBF found in subjects with anaemia and polycythaemia are primarily physiological and not caused by the accompanying alterations in blood viscosity. It is proposed that the response of the cerebral circulation to arterial oxygen content is mediated by a local mechanism sensitive to alterations in local tissue oxygen tension.

INTRODUCTION

The role of oxygen in relation to the cerebral circulation in man has usually been investigated by studying the effects of reducing the inspired concentration of oxygen on cerebral blood flow (CBF). One striking finding both in man and the dog is that this does not result in an increase in CBF until the arterial partial pressure of oxygen (pO_2) falls below about 50 mmHg (5.7 kPa) (Lassen, 1959; Shimojyo *et al.*, 1968; Kogure *et al.*, 1970). This implies that the cerebral circulation is responding to changes in arterial oxygen content rather than directly to the level of arterial pO_2. The oxygen content of blood depends mainly on the volume bound to haemoglobin, together with a relatively small amount dissolved in the plasma (Finch and Lenfant 1972). The volume bound to haemoglobin is determined by the concentration of haemoglobin and the degree to which it is saturated with oxygen. Because of the sigmoid shape of the oxygen dissociation curve a fall in arterial pO_2 does not cause a significant reduction in the saturation of haemoglobin and therefore in arterial oxygen content until a level of about 50 mmHg is reached. The coincidence of this figure with the threshold pO_2 below which CBF begins to fall in hypoxia is in favour of arterial oxygen content being the relevant determinant of CBF. This is supported by the finding that the rate at which oxygen is transported to the brain (the product of CBF and arterial oxygen content) in normocapnic hypoxia is maintained at normal levels (Lassen, 1982). If this interpretation is correct, then changes in arterial oxygen content resulting only from changes in haemoglobin concentration without changes in blood gases should also result in alterations of CBF so as to maintain a constant level of transport of oxygen to the brain. To determine if this is so we have studied the effects of variations in arterial oxygen content on CBF and cerebral oxygen transport in 54 subjects with a very wide range of haemoglobin concentrations varying from extreme anaemia to severe polycythaemia.

Pathological alterations in haemoglobin concentration are known to result in alterations of CBF, but the mechanism of the changes has been the result of considerable discussion. Polycythaemia is associated with a significant reduction in CBF (Kety, 1949; Nelson and Fazekas, 1956; Thomas *et al.*, 1977*a*) and at least some anaemic subjects have increased CBF (Scheinberg, 1949; Heyman *et al.*, 1952; Gottstein, 1978). *In vitro*, packed cell volume (PCV) is the major determinant of whole blood viscosity (Begg and Hearns, 1966) and patients with polycythaemia therefore have an increase in whole blood viscosity, while anaemic subjects have reduced values. Venesection lowers blood viscosity and increases CBF in subjects with polycythaemia (Thomas *et al.*, 1977*a*). Thomas *et al.* (1977*b*) also found low CBF values in subjects with PCV values at the upper end of the normal range and that CBF could be increased markedly by venesection. It was therefore suggested at the time that blood viscosity was an important determinant of CBF even in subjects with normal haemoglobin concentrations. Although less extensively studied, the increase in CBF in anaemia has also been attributed to a reduction in blood viscosity

TABLE 1. CLINICAL DIAGNOSES IN 54 SUBJECTS WITH HAEMOGLOBIN CONCENTRATION RANGING FROM 5.7 TO 19 1 g/dl

Diagnosis	*No. of subjects*
Polycythaemia rubra vera*	6
Idiopathic erythrocytosis*	4
Apparent polycythaemia*	10
Iron deficiency anaemia	15
Myeloproliferative disorders	6
Aplastic anaemia	5
Haemolytic anaemia	1
Lymphoma	1
Idiopathic thrombocytopenic purpura	1
Normal haematology	5

* The diagnoses in the polycythaemic subjects were based on the criteria outlined by Wetherley-Mein and Pearson (1982).

(Gottstein, 1978). On the other hand, Paulson *et al.* (1973) and Henriksen *et al.* (1981) have suggested that changes in oxygen availability are more important than changes in blood viscosity in determining CBF after haemodilution in subjects with normal or high haematocrits. Measurements of blood viscosity were therefore included in the current study so that the relationship between blood viscosity and CBF could be re-examined in more detail.

SUBJECTS

Fifty-four subjects were studied encompassing a wide range of haemoglobin concentration from 5.7 to 19.1 g/dl (mean 12.7, SD 4.1 g/dl). The clinical diagnoses encountered in the subjects are given in Table 1. Five of the subjects were haematologically normal, while the remainder had conditions leading to anaemia (29 subjects) or polycythaemia (20 subjects). The majority were attending a haematology outpatient department and none had neurological or other conditions likely to affect their level of CBF. None of the subjects had significantly raised plasma proteins, white cell or platelet counts. Vitamin B_{12} or folate deficiency was excluded by appropriate investigation. Twenty-two of the subjects were male. The average age was 55.6 (SD 13.8) years with a range of 18 to 77 years.

All the subjects gave their informed consent to the studies which were approved by the Ethics Committee of the National Hospitals for Nervous Diseases.

METHODS

Cerebral Blood Flow

This was measured by the noninvasive intravenous xenon^{133} clearance technique, described by Thomas *et al.* (1979). A bolus of approximately 7 mCi of xenon^{133} was injected into a forearm vein of the recumbent subject breathing room air and the clearance of the isotope from the cerebral hemispheres monitored with six external scintillation detectors (25 mm in diameter). Expired concentrations of xenon^{133} were monitored with a seventh detector and the end tidal levels used to estimate recirculating arterial xenon^{133} concentrations. Regional CBF was calculated from bicompartmental analysis of 11.5 min of the clearance curve according to the method of Obrist *et al.* (1975). This resulted in figures for perfusion through the fast clearing tissues of the brain, which are mainly grey matter. Allowance was made for the variation in the solubility of xenon in blood of different haemoglobin concentration using the formula derived by Veall and Mallett (1965). The value of CBF for each subject was taken as the mean of the six regional fast clearing tissue flows. Mean arterial blood pressure was recorded with a sphygmomanometer at the start of the CBF measurements.

Blood Gases

Blood gases were measured in heparinized samples taken at the end of each study under local anaesthetic from the brachial or radial artery. Measurements of arterial oxygen content were made in a Lex O_2 Con total oxygen content analyser (Lexington Instruments) or in an IL 282 CO-oximeter (Instrumentation Laboratories). In some of the anaemic subjects direct measurements of arterial oxygen content were contraindicated for reasons such as low platelet counts and in these cases arterial oxygen content was calculated from the venous haemoglobin concentration using the tables of Kelman and Nunn (1968). Arterial oxygen content calculated in this way correlated extremely well with direct measurements of arterial oxygen content in the 34 subjects of this study in whom both methods could be compared ($r = 0.982$, $P < 0.001$). Arterial carbon dioxide tension (pCO_2) was measured in an ABL 1 Acid-Base analyser (Radiometer, Copenhagen) or estimated from the expired end tidal concentration of carbon dioxide measured in a Datex CD 300 capnograph.

Blood Viscosity

Blood samples for viscosity measurements were taken at the time of the CBF measurement without stasis from an antecubital vein with the arm horizontal and the subject recumbent. Samples were anticoagulated with lithium heparin and the determinations made within 2 h. Whole blood and plasma viscosity were measured at 37° C in a Contraves LS 30 coaxial cylinder viscometer coupled to a Rheoscan 20 programmer and an XY recorder. The samples were subjected to a logarithmic increase in shear rate over a range of 0 to 128.5/s over a ramp time of 1 min. The figures given for whole blood and plasma viscosity were those calculated from the shear stress readings at a shear rate of 94.5/s

Haematology

Haemoglobin concentration was measured in a Coulter haemoglobinometer.

Cerebral Oxygen Transport

Cerebral oxygen transport was calculated for each subject from the product of their CBF and arterial oxygen content measurements *viz*:

cerebral oxygen transport = CBF × arterial oxygen content.

The derived figure therefore represents the rate at which oxygen was transported to a unit weight of brain in that subject. Measurements of the uptake of oxygen by the tissues (the cerebral metabolic rate) were not made in these studies because this would have required measurements of jugular venous pO_2, which was not considered ethical.

RESULTS

The first major finding of the study was that within the group of 54 subjects there was a close inverse relationship between arterial oxygen content and CBF, which is illustrated in fig. 1. The CBF response to variations in arterial oxygen content

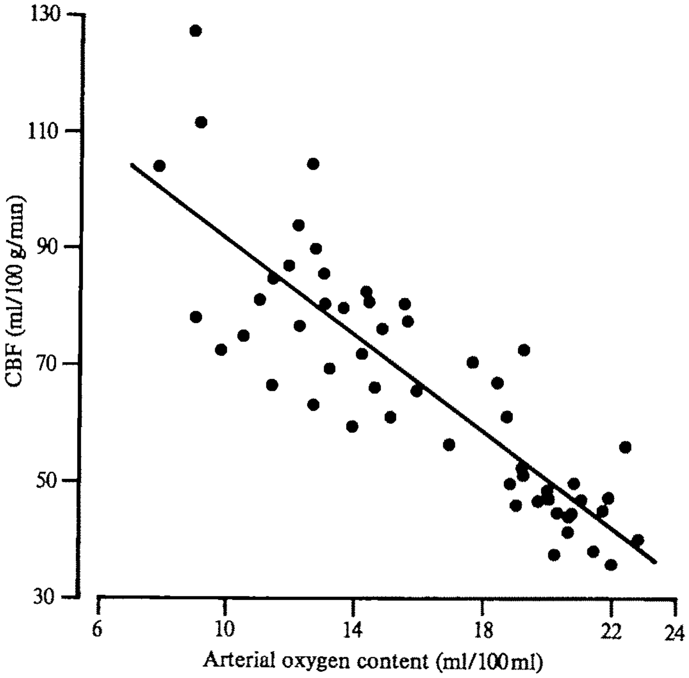

FIG. 1. Relationship between arterial oxygen content and cerebral blood flow (CBF) in 54 subjects.

appeared to be linear throughout the range and the correlation coefficient (r) between the two variables was highly significant at -0.855 ($P < 0.001$). The hypothesis that these changes in CBF occurred in order to maintain a constant level of transport of oxygen to the brain was examined by plotting CBF against the reciprocal of arterial oxygen content, since

$$\text{cerebral oxygen transport} = \text{CBF} \times \text{arterial oxygen content}$$

and if

$$\text{cerebral oxygen transport} = \text{a constant, k}$$

then

$$\text{CBF should} = \frac{1}{\text{arterial oxygen content}} \times \text{k}.$$

Fig. 2 illustrates that indeed there was a close linear relationship between CBF and the reciprocal of arterial oxygen content with a highly significant correlation coefficient of 0.831 ($P < 0.001$). Fig. 3, in which cerebral oxygen transport has been plotted against each subject's haemoglobin concentration, confirmed that cerebral oxygen transport remained constant within certain limits throughout the range of haemoglobin concentration encountered. The correlation coefficient r, in this figure was 0.044 (n.s.).

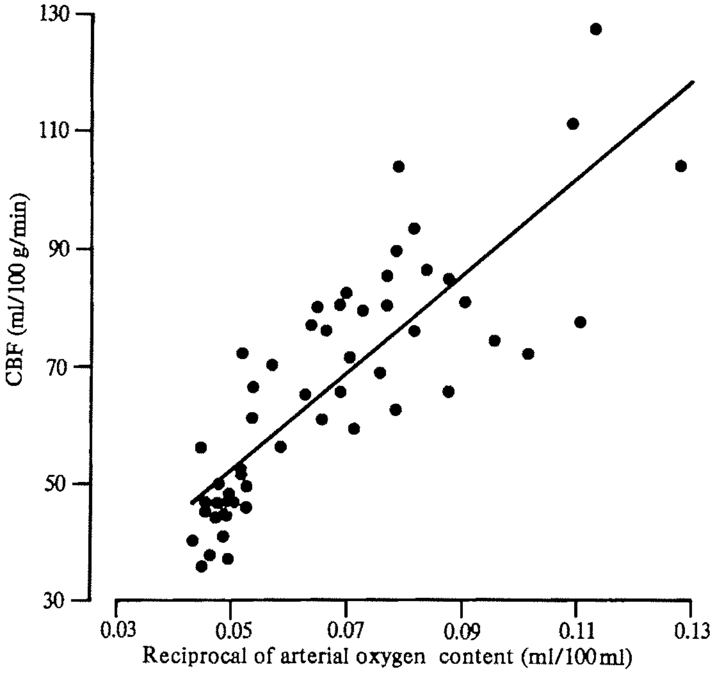

FIG. 2. Relationship between the reciprocal of arterial oxygen content and cerebral blood flow (CBF) in 54 subjects.

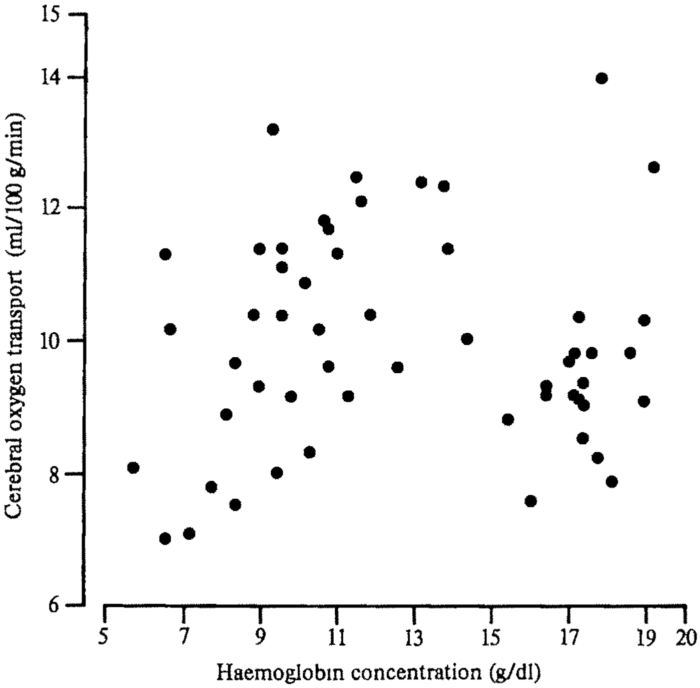

FIG 3. Relationship between haemoglobin concentration and cerebral oxygen transport in 54 subjects.

The relationship found within the group between CBF and the individual measurements of whole blood viscosity is illustrated in fig. 4. Overall there was a significant correlation between CBF and whole blood viscosity ($r = -0.802$, $P < 0.001$), but the relationship appeared to flatten out at higher viscosity values, so that above a viscosity value of about 5 mPa.s there was no discernible relationship between CBF and whole blood viscosity. There was also no significant relationship between cerebral oxygen transport and whole blood viscosity ($r = 0.027$). This is illustrated in fig. 5.

To determine the relative contribution to the level of CBF of the different parameters measured in the study, a multiple regression analysis of the results was carried out. A forward unconstrained stepwise inclusion technique was used as described by Nie *et al.* (1975). A summary of the results is presented in Table 2. The analysis confirmed that the majority of the variation in CBF in the group as a whole could be explained solely as a consequence of the differences in arterial oxygen content between the subjects. Variation in the other parameters did not appear to contribute significantly to the level of CBF. In particular, blood viscosity did not emerge as a significant determinant of CBF after the effects of arterial oxygen content had been taken into account. There was therefore no statistical evidence of

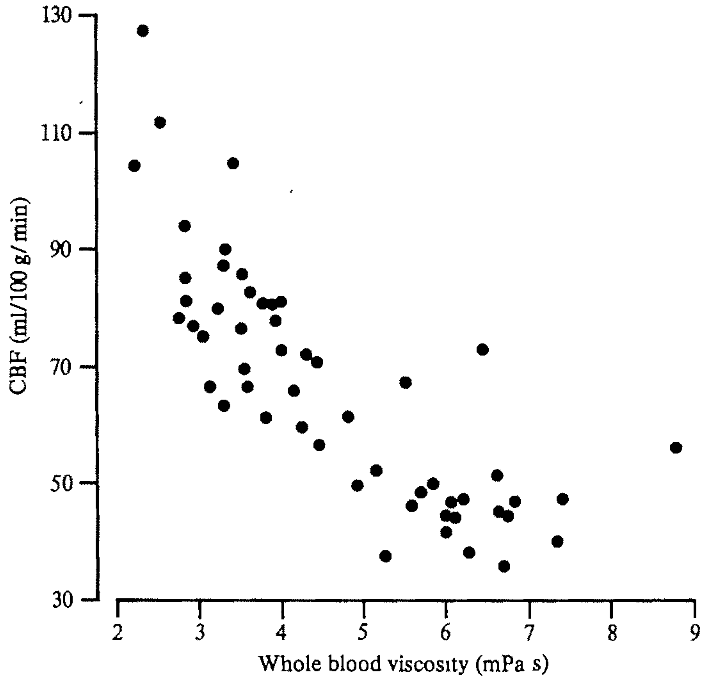

FIG. 4. Relationship between whole blood viscosity (measured at a shear rate of 94.5/s) and cerebral blood flow in 54 subjects.

an independent effect of whole blood viscosity on CBF and the analysis suggested that the simple regression between CBF and whole blood viscosity (illustrated in fig. 4) could be interpreted as reflecting the close correlation ($r = 0.937$, $P < 0.001$) between measurements of whole blood viscosity and arterial oxygen content. The analysis also demonstrated that the results could not be explained by variations in pCO_2, age or blood pressure.

TABLE 2. RESULTS OF MULTIPLE REGRESSION ANALYSIS OF THE DETERMINANTS OF CBF IN 54 SUBJECTS

Dependent variable	*Variable entered*	*F value to enter or remove*	*Significance*	*Multiple r*
Cerebral blood flow	Arterial oxygen content	15.19	$P = < 0.001$	0.855
	Arterial pCO_2	0 07	n.s.	0 856
	Age	0.32	n.s.	0.859
	Mean arterial BP	0 71	n s.	0 861
	Whole blood viscosity	0.01	n.s.	0.861

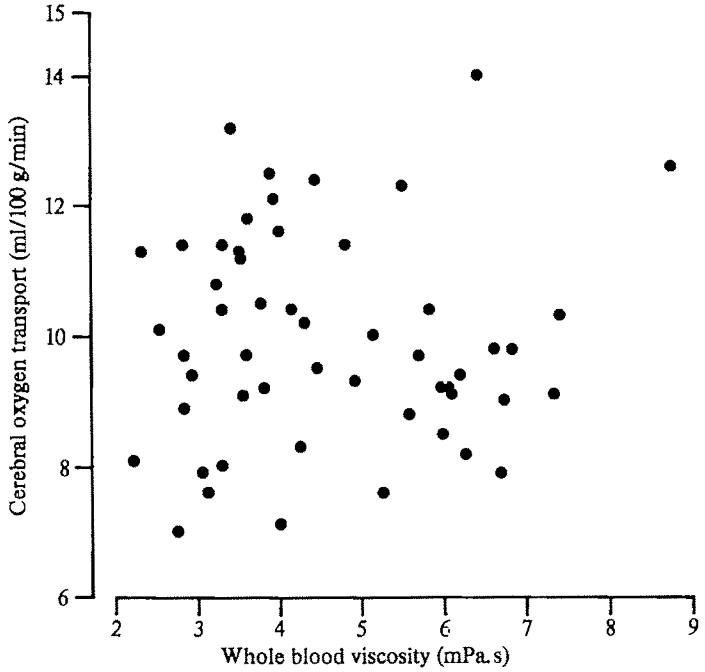

FIG. 5. Relationship between whole blood viscosity (measured at a shear rate of 94 5/s) and cerebral oxygen transport in 54 subjects.

DISCUSSION

These studies have confirmed that arterial oxygen content appears to be of fundamental importance in the regulation of CBF in man and that the changes in CBF in polycythaemia and anaemia can be explained as a physiological response to the alterations in arterial oxygen content in these conditions. CBF was measured in subjects with a very wide range of arterial oxygen content values and throughout this range CBF altered to maintain the rate of transport of oxygen to the brain within certain limits. The results could not be explained by variations in pCO_2, blood pressure or age. There was also no evidence that the changes in CBF were the result of the accompanying alterations in blood viscosity.

The direct application of measurements of blood viscosity *in vitro* to the circumstances *in vivo* has a number of limitations (Brown, 1984). In particular, measurements *in vitro* are made at a uniform shear rate while within the circulation shear rates are continually varying. However, the shear rate used in the current studies was representative of the high shear rates operating within the majority of the cerebral circulation (Whitmore, 1967). At such shear rates blood behaves as a newtonian fluid and its viscosity is independent of the shear rate. It is also necessary to establish that flow conditions within the circulation are appropriate for blood viscosity to influence significantly energy losses, but there are good reasons for believing that this is the case within the microcirculation (Caro *et al.*, 1978). In addition, measurements of blood viscosity on mixed whole blood samples may not be directly relevant to the behaviour of blood within the smallest capillaries where there is only room for red cells to travel in single file. Despite these limitations it is reasonable to assume that the very wide range of blood viscosity encountered in the current studies was indicative of corresponding, but not necessarily identical, differences within the circulation. If these changes in blood viscosity were to have had an overriding effect on CBF in our subjects, increasing blood viscosity would have been associated with a fall in cerebral oxygen transport, whereas no such effect was evident. Similarly, blood viscosity should have emerged as a significant factor in the multiple regression analysis of the determinants of CBF, while in fact only arterial oxygen content did so. Nevertheless, there was a significant inverse correlation between CBF and blood viscosity in the 54 subjects but this was only obvious at low viscosity values and could be explained as a coincidence resulting from the correlation between the measurements of blood viscosity and arterial oxygen content.

The conclusion that changes in arterial oxygen content result in physiological alterations in CBF is consistent with the results of several previous studies on the effects of oxygen on the cerebral circulation. Paulson *et al.* (1973) reported that inhalation of carbon monoxide, which caused a reduction in arterial oxygen content without changes in arterial pO_2 or blood viscosity, resulted in a reciprocal increase in CBF in normal subjects and were among the first to suggest that arterial oxygen content was an important determinant of CBF. We have already referred in the Introduction to the earlier evidence that the effects of alterations in arterial pO_2 on CBF are best interpreted as resulting from the accompanying changes in arterial oxygen content. More recently, Jones *et al.* (1981) have studied the effects of alterations both in arterial pO_2 and PCV on CBF in the lamb and also concluded that the results were best interpreted as a response to changes in arterial oxygen content.

The suggestion that variation in blood viscosity was not a significant determinant of CBF in our subjects is supported by our earlier finding that a reduction in blood viscosity achieved by plasma exchange without alterations in haemoglobin concentration or arterial oxygen content does not result in a significant change in CBF in haematologically normal subjects (Brown and Marshall, 1982). In this earlier study blood viscosity was reduced by plasma exchange to values equivalent to those of the anaemic subjects in the current study with haemoglobin concentrations of about 10 g/dl. We have also found that increases in blood viscosity equivalent or even greater than those occurring in our polycythaemic subjects, but resulting from increases in plasma viscosity or white cell count and therefore occurring without parallel increases in arterial oxygen content, do not by themselves result in a fall in CBF (Brown, 1984; Brown and Marshall, 1984).

Our conclusions contrast with those of the studies of Thomas *et al.* (1977*a*, *b*). The major evidence from these earlier studies for a deleterious effect of increasing blood viscosity was the finding that CBF in subjects with PCV values at the upper end of the normal range could be increased by venesection more than would be expected from the change in haemoglobin concentration. However, subsequent studies have not entirely confirmed this finding. Henriksen *et al.* (1981) found a less marked effect of haemodilution on CBF in otherwise normal subjects with high PCV and in particular did not find that this resulted in any increase in cerebral oxygen transport. Wade (1983) also found that cerebral oxygen transport was not increased by venesection in some subjects with polycythaemia, although in other subjects venesection led to a small but significant increase in cerebral oxygen transport, which could be interpreted as implying a small adverse effect of increased blood viscosity in these particular subjects. There is strong evidence from other studies, however, that the capacity to increase CBF in subjects with high PCV is not normally limited by the associated increase in blood viscosity. Polycythaemic subjects are able to increase CBF normally in response to inhalation of CO_2 and subjects with secondary polycythaemia due to hypoxic lung disease have nearly normal CBF despite elevated blood viscosity (Wade, 1981; Wade *et al.*, 1981). In addition, subjects with secondary polycythaemia resulting from the presence of a high oxygen affinity haemoglobin variant have a higher than normal CBF despite increased whole blood viscosity, emphasizing the importance of oxygen availability in the determination of CBF (Wade *et al.*, 1980). Part of the difference in the magnitude of the response to venesection reported by Thomas *et al.* and later authors may have occurred because of different subject selection and small numbers. In the study by Thomas *et al.* (1977*b*) on patients with high normal haematocrit, subjects with lower CBF were more likely to be venesected because the aim of the investigation was to see if CBF improved on lowering PCV. It is probable that if subjects with initially higher CBF had been included in the study, a less marked overall increase in flow would have been obtained (D. J. Thomas, personal communication). In the study on polycythaemia (Thomas *et al.*, 1977*a*) the numbers were small and the majority of the patients had vascular disease. It is known that physiological regulating mechanisms may be impaired in patients following stroke and CBF may then passively follow changes in perfusion pressure (McHenry *et al.*, 1974). It seems likely that under such circumstances flow would also passively follow changes in blood viscosity. It is therefore possible that increased blood viscosity was a factor limiting flow in some of the subjects of the earlier studies by Thomas *et al.* because their regulatory mechanisms were impaired by vascular disease. The current studies excluded subjects with established cerebrovascular disease and our conclusions are only likely to be applicable to subjects with normal vasculature.

A number of possible mechanisms could mediate the response of the cerebral circulation to alterations in arterial oxygen content. The most likely would be some form of local mechanisms sensitive to alterations in local tissue pO_2, designed to maintain this constant. The amount of oxygen released into the tissues at any one point in a capillary will be determined primarily by the flow rate, the oxygen content of the blood and the oxygen affinity of haemoglobin at the prevailing pO_2. Arterial oxygen content will therefore be a critical determinant of the total amount of oxygen released into the tissues. If the flow rate and tissue oxygen consumption remain constant, a change in arterial oxygen content will result in a similar change in mean tissue pO_2 (Garby and Meldon, 1977). There is considerable evidence from animal studies that local mechanisms exist to control CBF in response to changes in metabolism, such that a change in the local consumption of oxygen will result in a parallel change in local blood flow (Reivich, 1974; Sokoloff, 1981). Similarly, it has recently been shown in man, using positron emission computerized tomographic scanning, that there is a close match between the level of regional oxygen consumption and regional CBF (Frackowiak *et al.*, 1980). This local coupling between oxygen consumption and blood flow is probably mediated by an unidentified oxygen-dependent product of metabolism sensitive to local tissue pO_2 (Granger *et al.*, 1975). It would be economic for the same mechanism to mediate the alterations in CBF in response to changes in arterial oxygen content demonstrated in the current studies.

ACKNOWLEDGEMENTS

We would like to thank Professor G. Wetherley-Mein, Drs T. C. Pearson, R. W. Ross Russell, J. D. M. Richards and D. J. Thomas for their support and advice and for referring patients for study. Miss Sheila Redmond kindly assisted with the CBF measurements, Mr E. Zilkha tirelessly maintained the CBF equipment and Miss Beryl Laatz provided expert assistance in the preparation of the typescript. J.P.H.W. was supported by the Endowments Fund of St Thomas' Hospital and M.M.B. by a project grant from the Medical Research Council. Statistical advice was given by Miss L. Paul.

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(*Received November 8, 1983. Revised June 26, 1984. Accepted August 3, 1984*)

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WEIGHT APPRECIATION IN THE HAND IN NORMAL SUBJECTS AND IN PATIENTS WITH LEPROUS NEUROPATHY

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SUMMARY

The Weber fraction was used as an index of the sensitivity with which subjects appreciated weights ranging from 20 to 500 g suspended from the middle finger. Normal subjects were able to appreciate weight when it caused cutaneous compression alone. The sensitivity increased when subjects lifted weights by flexing the metacarpophalangeal joint. This increase was more marked for weights ranging from 20 to 100 g than for weights ranging from 200 to 500 g. When subjects lifted weights by flexing the elbow joint, the sensitivity with which they appreciated weight was comparable to that from cutaneous compression alone. Leprous subjects having glove anaesthesia were unable to appreciate any weight up to 500 g when it caused cutaneous compression alone. However, they were able to appreciate weights above 200 g when they lifted weights by flexing the metacarpophalangeal or elbow joints.

INTRODUCTION

Appreciation of force or tension is one of the aspects of kinaesthesis (Goldscheider, 1889; Roland and Ladegaard-Pedersen, 1977). The possible contributions to force appreciation are derived from the afferents of the skin, joints and muscles and from the 'sense of effort' (Merton, 1964; Gandevia and McCloskey, 1977*b*, *c*). A considerable amount of work has been undertaken in recent years to evaluate the ability of human subjects to appreciate weight and to discriminate between different magnitudes of weight (McCloskey *et al.*, 1974; Gandevia and McCloskey, 1976, 1977*a*, *b*, *c*, 1978; Roland and Ladegaard-Pedersen, 1977; Gandevia, 1978, 1982; Marsden *et al.*, 1979; Gandevia *et al.*, 1980). Yet the relative importance of various sources of information such as the afferents from the skin, joints and muscles and the 'sense of effort' contributing to the complex sensation of weight appreciation is by no means fully understood (McCloskey, 1978; Matthews, 1982). For example, Gandevia and McCloskey (1977*a*, *b*, *c*) held the view that in order to perceive the heaviness of a lifted object, human subjects depend more on the centrally-generated motor command than on the afferent response evoked by the weight itself. On the other hand, Roland and Ladegaard-Pedersen (1977) concluded that information contributing to accurate appreciation of the force is derived from the afferents of the muscles and tendons. Marsden *et al.* (1979) emphasized the need to seek more experimental evidence in order to evaluate the relative importance of various sources of information contributing to the complex sensation of weight appreciation. One of the aims of the experiments of this paper is to meet such a need.

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Phillips and Porter (1977) pointed out that a better insight into this problem could be obtained by studying the sensations present in subjects having chronic anaesthesia. The kinaesthetic sensation of weight appreciation has therefore been assessed in normal subjects and compared with that in patients with leprous neuropathy.

METHODS

All experimental procedures were described to the subjects and their consent obtained. The subjects ranged in age from 17 to 40 years and comprised normal controls and patients with chronic anaesthesia of the hand due to leprous neuropathy. The leprous subjects were stabilized on treatment, had no ulcers on their hands and were not in reactions such as down-grading, reversal or erythema nodosum leprosum (Waters *et al.*, 1971). Their hands were insensitive to touch (tested with no. 5 nylon, 2.5 cm long) and pressure (tested with a steel wire which had a bending force of 100 g). This lack of sensation extended in a glove distribution up to levels above the wrist. Standard clinical tests of muscle power (Mayo Clinic, 1976) showed that the extrinsic hand muscles were normal while the power of the intrinsic hand muscles was severely affected. Injection of 3 per cent saline into the belly of the flexor digitorum superficialis produced pain (Lewis, 1938) and the tonic vibration reflex was elicited from the forearm muscles.

The right hand and forearm of the subjects were positioned as illustrated in fig. 1. A basic weight was applied to the middle phalanx of the middle finger. Subjects could estimate this weight (1) from the sensation produced by passive compression of the skin (Experiment I); (2) by actively flexing the metacarpophalangeal joint, all other joints below and above, including the elbow, being immobilized with splints (Experiment II); or (3) by actively flexing the elbow joint, all other joints of the forearm and hand being splinted (Experiment III).

The subject was blindfolded and all audible clues were eliminated. The applied basic weight was altered and the just noticeable difference estimated. The chance factor in the subjects' reports was accounted for by the use of appropriate statistical methods. The applied basic weights ranged from 20 to 500 g for both normal and leprous subjects. The just noticeable difference divided by the corresponding basic weight gave the Weber fraction and was expressed as a percentage. The paired t test was used to compare the results obtained from each subject when using different modes of estimating the applied weight (Experiments I, II or III). The t test was used to compare the results obtained from leprous subjects with those from normals.

RESULTS

Appreciation of weight applied to the hand when the afferents from the skin and subcutaneous tissues alone were active was studied in normal subjects following the procedure described under Experiment I in Methods. The results are presented in the first rows of Tables 1 and 2. The sensitivity of appreciation of small weights (20–60 g) is very low (Weber fractions ranging between 89 and 35%). As the basic weight increases, the Weber fraction decreases and remains relatively constant at weights above 200 g.

An increased afferent input was achieved by the experimental design described under Experiment II in Methods. Active changes in length of the extrinsic and intrinsic hand muscles as well as movement of articular tissue were obtained in this experiment. The second rows of Tables 1 and 2 give the results obtained for the normal subjects. Again, it is noteworthy that the Weber fraction decreases as the basic weight increases, reaching a relatively constant value at weights above 200 g. It is clear that the Weber fraction is significantly decreased when there is active movement of the fingers, especially when small weights (20–60 g) were used ($P < 0.025$, paired t test). The best sensitivity of weight appreciation was achieved when the weight suspended from the finger was actively lifted by digital movement (i.e. flexion of the metacarpophalangeal joint—Experiment II). When the weight suspended from the finger was lifted by flexing the elbow joint as described in Experiment III, active changes in length of upper arm muscles as well as movement of articular tissues of the elbow joint were obtained. In this experiment, the sensitivity of weight appreciation was comparable to that in Experiment I ($P < 0.025$, paired t test).

Leprous subjects were unable to perceive weights of up to 500 g under the conditions described in Experiment I, or below 100 g under the conditions described

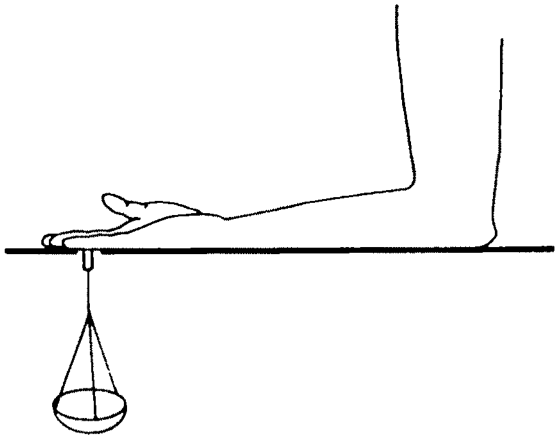

FIG. 1. Position of the upper limb in all experiments. In Experiment I, the elbow, wrist, metacarpophalangeal and the proximal and distal interphalangeal joints of the middle finger were immobilized with splints. The subject estimated the weight without using any lifting effort. In Experiment II, the elbow, wrist and the proximal and distal interphalangeal joints were immobilized with splints. The subject lifted the weight by flexing the metacarpophalangeal joint. In Experiment III the wrist, metacarpophalangeal and the proximal and distal interphalangeal joints were immobilized. The subject lifted the weight by flexing the elbow joint.

TABLE 1 NORMAL SUBJECTS BASIC WEIGHT *VS* WEBER FRACTION

	Basic weight (g)					
	20	*40*	*60*	*80*	*100*	*200*
Experiment I						
Mean Weber fraction (%)	89.29	43.93	35.47	28.09	25.71	22.92
± SE	6.94	9.45	10.88	8.80	7.54	6.36
Range	60.0–100.0	30.0–100.0	20.0–100.0	13.3–80.0	12.0–70.0	11.0–60.0
Experiment II						
Mean Weber fraction (%)	27.86	19.24	15.00	13.27	12.00	12.00
± SE	3.91	3.96	2.70	2.08	1.76	1.77
Range	20.0–50.0	12.5–42.2	10.0–30.0	9.0–23.3	8.0–20.0	8.0–20.0
Experiment III						
Mean Weber fraction (%)	84.29	50.70	40.23	32.51	27.43	21.00
± SE	7.59	8.64	10.30	8.34	7.62	5.91
Range	55.0–100.0	32.5–100.0	20.0–100.0	13.3–80.0	12.0–70.0	10.0–55.0

No. of subjects = 7.

in Experiments II and III. However, they were able to perceive weights above 100 g in Experiments II and III (*see* Table 3). Weber fractions obtained from leprous subjects in Experiment II were significantly higher than those obtained from normal subjects ($P < 0.025$, t test), and also significantly higher in Experiment III at weights of 100 and 200 g ($P < 0.025$). However, at higher weights (300–500 g), Weber fractions obtained from leprous subjects in Experiment III did not differ significantly from those obtained from the normals. It is remarkable that for the leprous subjects, the Weber fractions obtained in Experiment II were significantly greater than those obtained in Experiment III ($P < 0.025$, paired t test) (*see* fig. 2). On the contrary, for normal subjects the Weber fractions obtained in Experiment II were significantly lower than those obtained in Experiment III ($P < 0.025$).

TABLE 2. NORMAL SUBJECTS BASIC WEIGHT *VS* WEBER FRACTION

	Basic weight (g)					
	40	*100*	*200*	*300*	*400*	*500*
Experiment I						
Mean Weber fraction (%)	27.81	21.50	17.81	18.13	18.44	19.25
± SE	3.88	2.71	1.53	1.64	2.21	2.36
Range	15.0–50.0	17.0–40.0	12.5–25.0	11.7–23.3	10.0–30.0	8.0–30.0
n = 8						
Experiment II						
Mean Weber fraction (%)	16.07	12.43	11.07	10.38	9.87	10.14
± SE	1.96	0.78	0.55	1.08	0.77	1.03
Range	10.0–25.0	10.0–15.0	9.0–12.5	6.0–15.9	7.0–12.5	8.0–14.0
n = 7						
Experiment III						
Mean Weber fraction (%)	46.25	25.50	19.00	17.77	15.83	14.33
± SE	7.24	2.33	1.66	1.65	1.24	0.96
Range	25.0–75.0	16.0–30.0	12.5–25.0	13.3–23.3	12.5–20.0	10.0–16.0
n = 6						

TABLE 3. SUBJECTS WITH LEPROUS NEOPATHY

	Basic weight (g)					
	40	*100*	*200*	*300*	*400*	*500*
Experiment II						
Mean Weber fraction (%)	*	50.0**	43.49	36.31	37.96	33.55
± SE		4.99	4.15	3.01	3.57	3.16
Range		30.0–65.0	20.0–60 0	20.0–50.0	20.6–55.0	16.0–50.0
n = 9						
Experiment III						
Mean Weber fraction (%)	*	50.00**	27.85	24.16	18.75	18.13
± SE		6.80	2.40	3.26	1.49	1.63
Range		30.0–80.0	20.0–40.0	13.3–40.0	12.5–30.0	10.0–25.0
n = 9						

* Subjects could not perceive the weight. ** Two subjects were unable to perceive this weight.

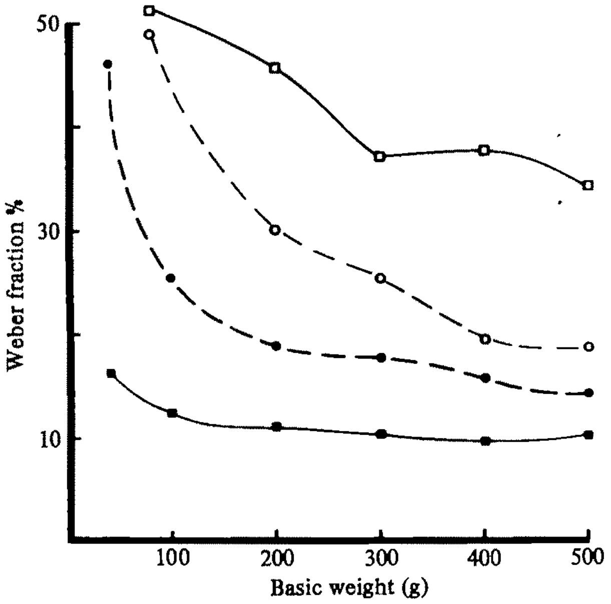

FIG. 2. Graph relating the basic weight to Weber fraction. Filled squares = Experiment II, normal subjects. Filled circles = Experiment III, normal subjects. Open squares = Experiment II, leprous subjects. Open circles = Experiment III, leprous subjects. Weber fractions obtained from leprous subjects were larger than those obtained from normal subjects in Experiment II. Moreover, normal subjects appreciated weights more sensitively in Experiment II than in Experiment III whereas leprous subjects appreciated weights more sensitively in Experiment III than in Experiment II.

DISCUSSION

Force appreciation is a part of kinaesthesis (Goldscheider, 1889). In this paper the ability of human subjects to discriminate between different magnitudes of weights has been studied. The weights used are considerably smaller than those used by other authors (Gandevia and McCloskey, 1977*b*, *c*; Roland and Ladegaard-Pedersen, 1977). This is because it is presumed that fine manipulative movement of the digits involve forces of such magnitudes and consequently errors of judgement will be of corresponding orders of magnitudes. The results indicate that weights less than 100 g require afferent inputs which arise from various anatomical locations such as skin, joints and muscles. This conclusion has been reached because cutaneous compression alone (Experiment I) gives rise to force appreciation, but with low discriminative ability. Active movement of the digit increases the sensitivity of force appreciation significantly (Experiment II).

Leprous subjects having chronic anaesthesia of the hand were unable to appreciate weights less than about 100 g, even although many sources of afferents from the upper limb were called into play. The sensory deficit in these subjects were largely restricted to the hand. This deficit included afferents from the skin and presumably those from the grossly wasted intrinsic hand muscles. It is likely that the articular afferents from the digits were also lost. The afferents arising from the extrinsic hand muscles were presumed to be largely normal, based on the results of pain elicited by the injection of 3 per cent sodium chloride solution, the tonic vibration reflex and tendon jerk. This suggests that afferents from the hand are required for appreciation of these forces: afferents arising from the extrinsic hand muscles cannot adequately sense these small forces applied to the digits.

From the results of the experiments described here, no one species of receptor can be described as playing a major role in the appreciation of small forces applied to the hand. In all probability a convergence of inputs from various types of receptors is necessary.

Variations in weights greater than 100 g were readily appreciated when cutaneous and subcutaneous afferents alone were activated. Movement of the digits significantly increases the sensitivity in all cases irrespective of the basic weight. Again, the results obtained from the subjects with leprous neuropathy indicate that receptors located in the extrinsic hand muscles are relatively insensitive to forces applied to the hand. It may therefore be concluded that the receptors located in the intrinsic hand muscles and the articular tissue of the hand contribute to this increase in sensitivity.

Results obtained from acutely anaesthetized hands tend to indicate that the kinaesthetic deficit is similar to that which remains in the chronically anaesthetic hand. This suggests that the subtraction of afferent inputs following anaesthesia of the hand cannot be compensated by a learning process. When the hands of normal subjects were made anaesthetic by ischaemia (Lewis *et al.*, 1931; Marsden *et al.*, 1971), it was found that the Weber fraction obtained at 200 g was comparable to that of leprous subjects using the same basic weight.

In recent years there have been many studies regarding the appreciation of weight or force applied to the hand (McCloskey *et al.*, 1974; Gandevia and McCloskey 1976, 1977*a*, *b*, *c*, 1978; Roland and Ladegaard-Pedersen, 1977; Gandevia, 1978, 1982; Marsden *et al.*, 1979; Gandevia *et al.*, 1980). The present study extends these by establishing that variations around forces smaller than about 100 g require active movement of digits to be sensitively appreciated. Discrimination around weights greater than 100 g can be obtained using cutaneous afferents alone. Active movement of the digits, however, significantly increases the sensitivity of discrimination.

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CEREBRAL SOMATOSENSORY POTENTIALS EVOKED BY MUSCLE STRETCH, CUTANEOUS TAPS AND ELECTRICAL STIMULATION OF PERIPHERAL NERVES IN THE LOWER LIMBS IN MAN

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SUMMARY

Somatosensory cerebral evoked potentials were recorded in man to natural forms of somatosensory stimulation of the lower extremity including stretching of the muscle tendons, tapping on muscle bellies and tapping on cutaneous surfaces. These potentials were compared with those evoked by electrical stimulation of peripheral nerves measuring the amplitudes and latencies of the evoked potential components and defining the effects of stimulus variables on these parameters. Spinal cord potentials could only be detected to electrical stimuli.

Mechanical stimulation of tendons and muscle bellies evoked scalp potentials at latencies earlier than those evoked by electrical stimulation of the peripheral nerve and by cutaneous stimulation at the same level of the leg. Muscle receptors, most probably muscle spindles, are the source of the short latency components obtained by the stretching of tendons and tapping on muscle bellies. The proximal location of these receptors as well as very rapid spinal conduction account for the latency difference.

The potentials were larger to electrical stimulation of nerve trunks than to mechanical stimulation of tendons or skin, suggesting the asynchronous activation of a smaller number of fibres by the latter. Individuals with the largest potentials to one form of stimulation usually had the largest potentials to the other modes of stimulation.

The use of physiological stimuli such as muscle stretch to test the transmission in specific neural pathways might be useful in investigating the processing of relatively selective afferent volleys using noninvasive evoked potential recordings.

INTRODUCTION

The recording of somatosensory evoked potentials (SEPs) has customarily employed percutaneous electrical stimuli to activate mixed or sensory nerves (Jones, 1982). In the last ten years several studies have demonstrated the possibility of eliciting evoked potentials to different types of natural stimulation: mechanical deformation of the skin of the finger (Pratt *et al.*, 1979*a*, *b*, *c*, 1980, 1981; Ishiko *et al.*, 1980; Pratt and Starr, 1981), flexion or extension of the ankle joint (Starr *et al.*, 1981) and thermal stimulation (Carmon *et al.*, 1978). These alternative methods have the advantage of (1) providing information about the function of the receptors and terminal nerve fibres which electrical stimulation of nerve trunks bypasses and (2) activating relatively specific types of neural elements and central pathways. The resulting evoked potentials, while of small amplitude, reflect the activity of a relatively homogeneous neural population compared with the potentials obtained after electrical stimulation of a mixed or even motor or sensory peripheral nerve. Clinical uses of naturally evoked somatosensory potentials have been infrequent due, in part, to their small amplitude but also to the lack of systematic knowledge of factors contributing to their latencies and amplitudes. This study examines in man the surface-derived cerebral potentials evoked by mechanical stimulation of tendons, muscles and skin at several levels of the lower limb, and compares natural potentials with the potentials evoked by the customary electrical stimulation of nerve trunks.

METHODS

Subjects

Evoked potentials were recorded in 8 healthy subjects (4 men and 4 women) aged 19 to 30 years. Informed consent was obtained for participation in the study. They were tested in a sound-attenuating chamber while reclining on a bed. The ankle and knee joints were fixed at 90 deg by a plastic mould to restrict movements during testing. Skin temperature of the foot was monitored and maintained between 31 and 35° C.

Stimulation and Recording Procedures

Percutaneous electrical stimulation with bipolar electrodes was performed over (1) the tibial nerve at the ankle immediately posterior to the medial malleolus; (2) the deep peroneal nerve at the ankle between both malleoli; (3) the sural nerve at the ankle immediately posterior to the lateral malleolus; (4) the tibial nerve at the popliteal fossa; (5) the common peroneal nerve at the head of the fibula; and (6) the femoral nerve at the inguinal ligament. The intensity of the stimuli was adjusted to elicit a just visible twitch of the appropriately innervated muscles without causing pain. The intensity for the sural nerve was three times the sensory threshold except in thin subjects in whom this intensity also activated the motor fibres of the tibial nerve. The stimulus to the sural nerve was diminished until the muscles of the foot no longer twitched.

Muscle stretch from mechanical stimulation of the tendon was produced by a moving coil vibrator. The spindle of the vibrator was attached to a T rod with the horizontal portion placed in contact with the tendon. Activation of the vibrator resulted in a downward rod movement of 4 to 5 mm. The sound produced by the vibrator was masked by white noise from a headphone applied over the ears of one subject. As there were no differences between recordings obtained with and without masking, it was not used during the rest of the study. For the Achilles tendon the site stimulated was 3 to 6 cm proximal to its insertion; the tendon of the tibialis anterior muscle was tapped at the ankle and the tendon of the quadriceps just below the patella at the insertion of the ligamentum patellae in the tibia. Mechanical stimulation of the muscle was produced by tapping on the skin overlying the middle of the belly of the lateral head of the gastrocnemius, the tibialis anterior and the rectus femoris. Mechanical stimulation of the skin was produced by tapping on the skin overlying the lateral malleolus and the tibial tuberosity, avoiding movements of the joints. The rod was placed 3 mm above the skin surface and activation of the vibrator resulted in a gentle 'tap'. All mechanical stimuli were produced by activating the moving coil vibrator with a 70 to 100 ms duration square wave pulse. In one subject displacement of the tendon was recorded with a force displacement transducer (FDT) attached in parallel with the rod. The onset of the displacement occurred between 1 to 3 ms after activating the vibrator and peak displacement occurred by 10 ms (fig. 1). Two sets of 700 stimuli were performed for each peripheral nerve stimulation. This number of trials resulted in 20 per cent or less amplitude difference in the scalp P1-N1 components on repeated measures in the same subject at the same session. Two sets of 2000 stimuli were required for each mechanical stimulus to fulfil this same standard.

SEPs were recorded between an electrode on the scalp at Cz (according to the 10-20 system) referenced to the forehead (Fpz). Electrode impedances were below 5 kΩ. The Fpz site was chosen as reference since it was relatively isopotential after 23 ms (Achilles tendon tap) or 26 ms (tibial nerve) when referred to a noncephalic reference such as the shoulder. Earlier components were detected, possibly reflecting activity in subcortical structures or spinal cord. Nerve root and spinal cord potentials to electrical stimulation were recorded between an electrode over L1 referenced to electrodes over L5 or the anterior superior spine of the iliac crest. However, no clear spinal potentials could be defined to mechanical stimulation even using 10 000 stimuli. Subjects were grounded by a metal plate strapped to the leg proximal to the knee.

The potentials were amplified with a gain of 500 000 using a band pass of 30-3000 Hz (6 dB/octave slope) and averaged over a 102.4 ms time period with a dwell time of 0.2 ms and 512 points per channel. A duplicate of each average was made to assess reproducibility. The averaged potentials were plotted (positivity at the 'active' electrode of the differential configuration was displayed in an upward direction) and stored for further analysis. Amplitudes and latencies of the various components of the recorded potentials were measured from a computer display with a cursor. Latencies were measured from the onset of the electrical pulse activating the peripheral nerve or the mechanical vibrator to the peak of the various components. Amplitudes were measured in one or both of two ways: (1) absolute amplitudes between baseline and positive or negative peaks; (2) differential amplitudes between the positive peak and immediately following negative peaks. The main intent of this paper is to compare the latencies and amplitudes of components evoked by different forms of stimulation at several sites along the leg (initial positivity, initial negativity, etc.). Since these components have different latencies for each of the 14 stimuli applied, we have designated the components with their polarity (P or N for positive or negative) and their sequence (i.e., 1, 2 for first, second, etc.). The t test for related measures between the means was performed to evaluate differences.

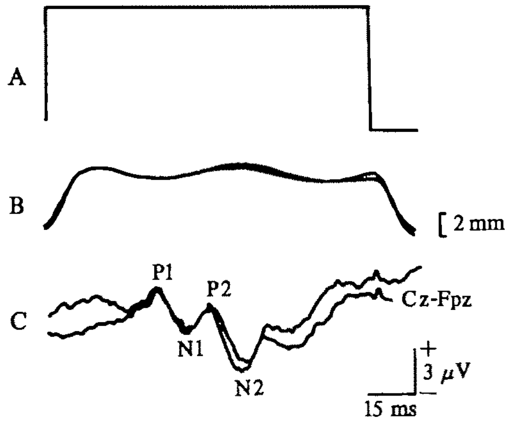

FIG. 1. A shows the stimulus pulse applied to the vibrator, B, the mechanical displacement of the tendon and C, two superimposed averages of cerebral evoked potentials (Cz-Fpz) to Achilles tendon tap stimulation. The components of the evoked potentials are labelled according to their polarity and sequence (P positive, N negative).

RESULTS

Mechanical deformation of the Achilles tendon evoked reproducible scalp potentials with an initial positive component peaking at 31.7 ± 3.1 ms (P1) followed by negative, positive, negative components at 43.5 ± 3.8 ms (N1), 53.5 ± 2.5 ms (P2) and 65.3 ± 4.5 ms (N2), respectively (fig. 1). There was a clear correlation between the latency of P1 component to both Achilles tap and tibial nerve stimulation at the ankle and body height in each subject. Fig. 2A shows these relationships in 11 subjects and fig. 2B the relation between P1 latencies to Achilles tap and to tibial nerve stimulation at the ankle. We concentrated our analysis on the initial positive-negative components and studied the influence of several stimulus variables on these components.

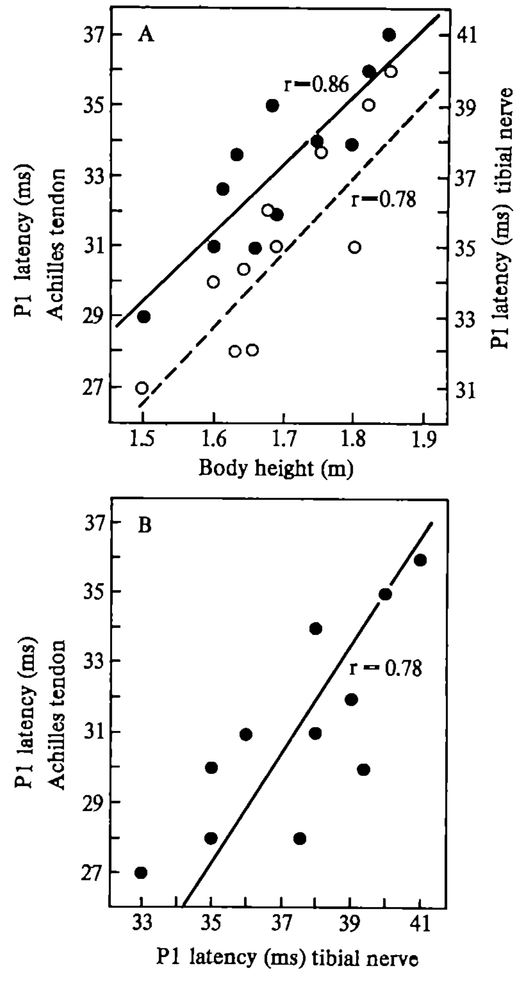

FIG. 2. A shows the relationship between height and P1 latency of the cortical potentials evoked by stimulation of the tibial nerve at the ankle (filled circles) and the Achilles tendon (open circles). In B, the relationship between P1 latencies to tibial nerve stimulation and to Achilles tendon tap stimulation are compared.

Effects of Stimulus Parameters

Repetition rate. In the one subject tested, the amplitude of the P1-N1 components decreased in a fairly linear manner as stimulus rate increased from 1 to 6 Hz (fig. 3A, C).

Intensity. As the extent of the vibrator excursion was reduced, the amplitude of the P1-N1 components decreased in the same subject (fig. 3B, C). The effective dynamic range of the stimulus over which the amplitude of the cortical potentials was affected was approximately 20 dB.

Rise and fall times. The rise time of the pulse applied to the vibrator changed the acceleration of the mechanical tap in the one subject tested and affected both the amplitude and latency of the evoked potentials. Slowing acceleration from 0.08 $m{\cdot}s^{-2}$ to 0.008 $m{\cdot}s^{-2}$ caused an increase in latency from 32 ms to 44 ms and 65 per cent diminution of amplitude (fig. 4A, C). It is interesting that for an acceleration faster than 0.035 $m{\cdot}s^{-2}$ the amplitude of P1-N1 did not change, whereas for an acceleration slower than 0.035 $m{\cdot}s^{-2}$ there was a profound

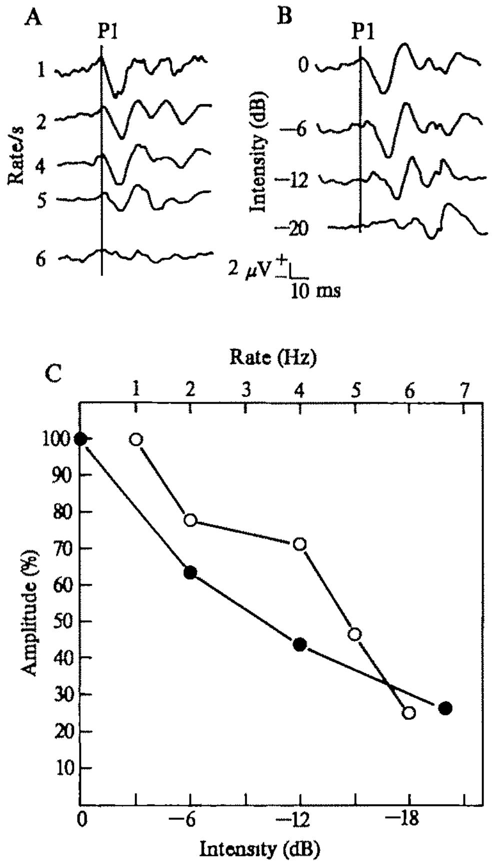

FIG. 3. A shows the effects of repetition rate and B, the intensity of the mechanical stimuli on the amplitude of Achilles tendon tap evoked potentials in one subject. The initial scalp positivity P1 is marked by a vertical line. In C, the graph shows the amplitude of the initial positive-negative complex (P1-N1) as a function of the repetition rate (open circles) and intensity of the mechanical taps (filled circles). The amplitude at the highest intensity (0 dB) and slowest rate (1 Hz) was set to be 100 per cent and the amplitudes of the other intensities and rates adjusted accordingly

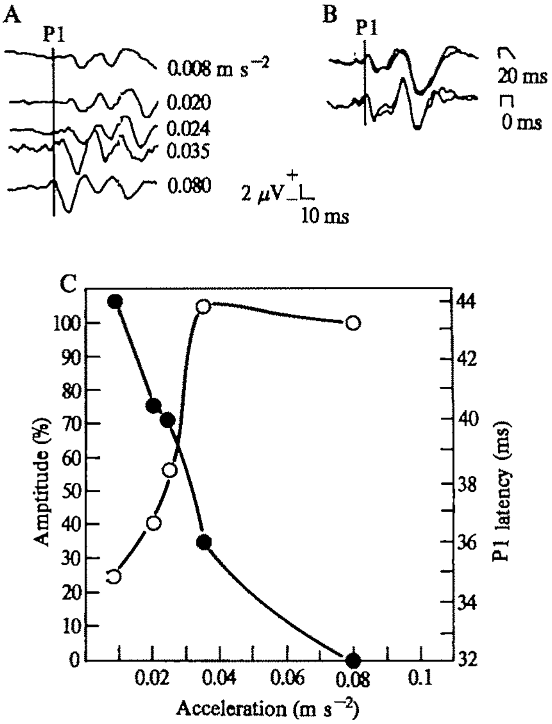

FIG. 4. Effects of changing the rise time (A) and fall time (B) of the pulse applied to the vibrator and consequently its acceleration and deceleration on potentials evoked by Achilles tendon taps in one subject. In C, the amplitude (filled circles) of the initial positive-negative component (P1-N1) and the latency (open circles) of the P1 component is plotted as a function of acceleration of the mechanical stimulus. Slowing acceleration increased the latency and diminished the amplitude of the evoked potentials while changing the deceleration of the taps had no effect.

decrement in amplitude. Changing the fall time of the pulse and thus the rate of release of the mechanical tap had no effect on the potentials since the components all occurred before the release (fig. 4B).

Site of stimulation. In one subject, taps were delivered at different positions along the longitudinal axis of the Achilles tendon beginning at the heel, extending up the tendon and ending on the gastrocnemius-soleus muscle belly (triceps surae) (fig. 5). Even though these stimuli were delivered over a 25 to 30 cm distance, their evoked potentials had the same conformation and latencies but some amplitude differences. The largest potentials were obtained when tapping on the Achilles tendon and the triceps surae muscle belly. The smallest were obtained when tapping at the union of the tendon and muscle or at the calcaneus bone.

Angular incidence of the tap. In one subject taps were delivered to the Achilles tendon at different angles of incidence in both the longitudinal and perpendicular axes (45, 90 and 135 deg) without affecting the amplitudes or latencies of the potentials.

Position of the subject. In one subject Achilles tap SEPs were recorded with the subject in three different positions: (1) lying prone ; (2) sitting on a chair; and (3) lying on his side. There were no consistent amplitude or latency differences between these recordings.

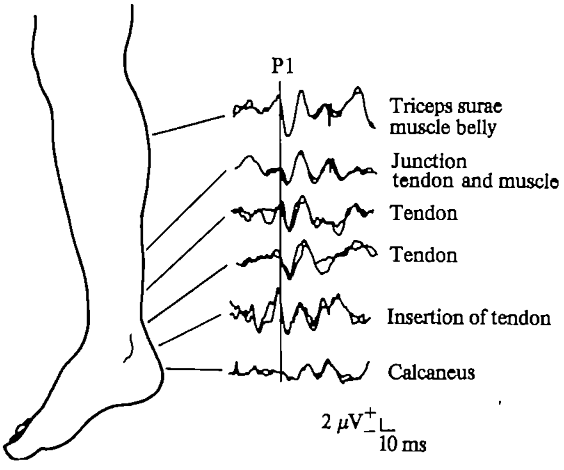

FIG. 5 Shows the effects of delivering taps at different positions along the longitudinal axis of the heel and calf in one subject on the evoked potentials recorded over the scalp (Cz-Fpz). The initial component of the potentials was maximal when stimulating the tendon or the muscle belly and minimal when tapping over the calcaneus The initial positivity, P1, is marked by a vertical line.

Replicability of the potentials. When the same subject was tested at different times on the same day as well as on different days the potentials had the same general morphology though their amplitude varied slightly (by less than 20%) (fig. 6).

Potentials Evoked by Mechanical Stimulation of Tendon, Muscle and Skin and by Percutaneous Electric Stimulation of Peripheral Nerves

Activation of the somatosensory system from the lower limb by several different methods, namely mechanical deformation of tendon, muscle, skin or electrical stimulation of nerve trunks, evoked similarly shaped potentials from the scalp.

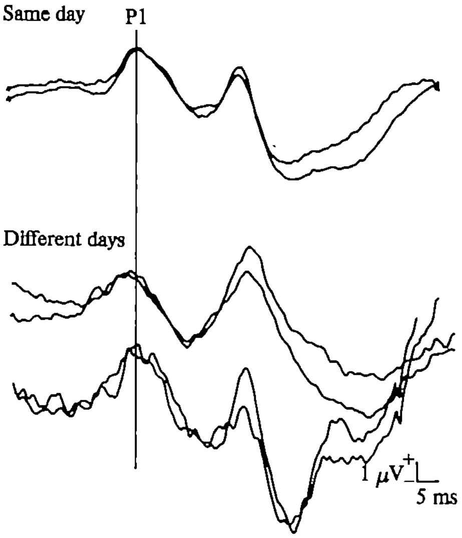

FIG. 6 Replicability of cerebral evoked potentials to Achilles tendon taps in two different sessions on the same day and on different days in the same subject. Each average consists of 2000 stimuli.

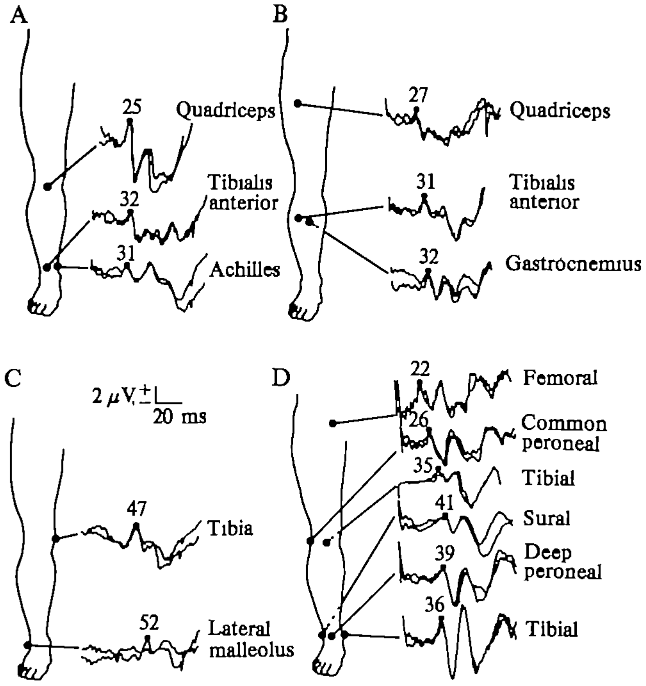

FIG. 7 Somatosensory potentials evoked by different stimuli in a single subject. A, mechanical stimulation of tendons. B, mechanical stimulation of muscle bellies. C, mechanical stimulation of skin overlying bone. D, electrical stimulation of nerves. The latencies of the P1 component recorded over the scalp (Cz-Fpz) to each form of stimulation is indicated over the peak. Averages of 700 stimuli for electrical stimulation and 2000 stimuli for mechanical stimulation are superimposed.

There was an initial positive peak followed by a sequence of alternating polarity components. Both the latencies and amplitudes of these components varied as a function of the level of the limb stimulated (e.g. ankle *vs* knee) as well as the particular type of somatosensory stimulus employed. Fig. 7 contains the averaged potentials from a single subject to the various stimuli applied to the ankle, knee and groin and fig. 8 the grand average from 8 subjects. The quantitative measures of latencies and amplitudes of these various potentials are in Table 1.

In summary, the amplitudes of the P1-N1 components evoked by electrical stimulation of the nerve trunks were considerably larger (4–10 μV) than those evoked by tendon taps (2–6 μV), muscle belly taps (1–2 μV) and cutaneous taps (2 μV). As would be expected, the latencies of the initial scalp positive component decreased as the site of stimulation on the lower limb was moved proximally.

Relation between Potentials Evoked by Mechanical Stimulation of the Tendon, Muscle and Skin and Potentials Evoked by Electrical Stimulation of Peripheral Nerves

Fig. 9 shows that stimulation at a given level of the leg, for example at the ankle, evoked potentials whose latencies differed in a systematic manner depending on the mode of stimulation. The latencies were shortest for tendon taps, intermediate for whole nerve stimulation and longest for cutaneous stimulation (*see also* Table 1).

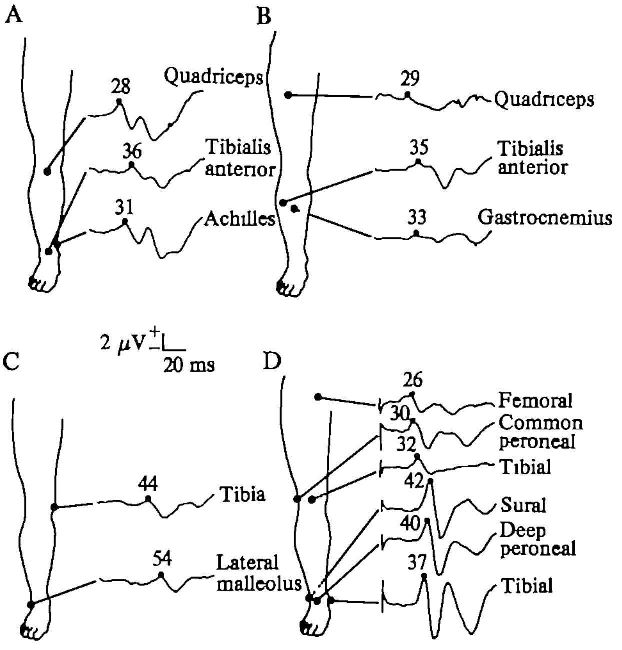

FIG. 8. Grand averages of potentials evoked by different stimuli in 8 subjects. A, mechanical stimulation of tendons. B, mechanical stimulation of muscle bellies. C, mechanical stimulation of skin overlying bone D, electrical stimulation of nerves. The latencies of the P1 component recorded over the scalp (Cz-Fpz) to each form of stimulation is indicated over the peak

TABLE 1 LATENCIES AND AMPLITUDES* OF P1 AND P1-N1 COMPONENT OF CEREBRAL POTENTIALS EVOKED BY VARIOUS SOMATOSENSORY STIMULI (8 SUBJECTS)

	P1			*P1-N1*	
	Latency	*Amplitude*	*% Amplitude*	*Amplitude*	*% Amplitude*
Nerves					
Tibial at ankle	37.5 ± 2.6	3.9 ± 2.1	100	10.0 ± 7.5	100
Sural at ankle	42.1 ± 1.4	4.2 ± 2.9	107	7.2 ± 7.9	71
Deep peroneal at ankle	40.8 ± 2.3	3.3 ± 2.0	84	8.3 ± 8.0	82
Tibial at popliteal fossa**	32.7 ± 2.1	2.1 ± 1.2	53	5.8 ± 4.0	58
Common peroneal at fibula	30.6 ± 3.3	2.8 ± 1.4	71	5.1 ± 5.4	51
Femoral at inguinal ligament	26.2 ± 3.0	1.9 ± 0.8	48	4.1 ± 3.2	41
Tendon taps					
Achilles	31.7 ± 3.1	1.1 ± 1.5	27	3.2 ± 3.1	32
Tibialis anterior	36.2 ± 2.6	0.3 ± 1.3	9	2.9 ± 2.4	29
Quadriceps	26.5 ± 3.6	2.2 ± 2.7	56	6.1 ± 5.7	60
Muscle taps					
Gastrocnemius	33.6 ± 2.7	0.7 ± 1.0	17	2.2 ± 2.6	21
Tibialis anterior	35.2 ± 3.8	1.1 ± 1.2	27	1.8 ± 2.7	18
Quadriceps	29.6 ± 5.1	0.5 ± 1.1	12	2.6 ± 2.1	26
Cutaneous taps					
Tibia	44.0 ± 11.3	0.4 ± 1.4	10	2.0 ± 1.5	20
Lateral malleolus**	54.1 ± 3.8	0.1 ± 0.8	3	1.9 ± 1.0	19

* The amplitude of potentials evoked by stimulation of the tibial nerve at the ankle was set at 100 per cent. ** n = 7

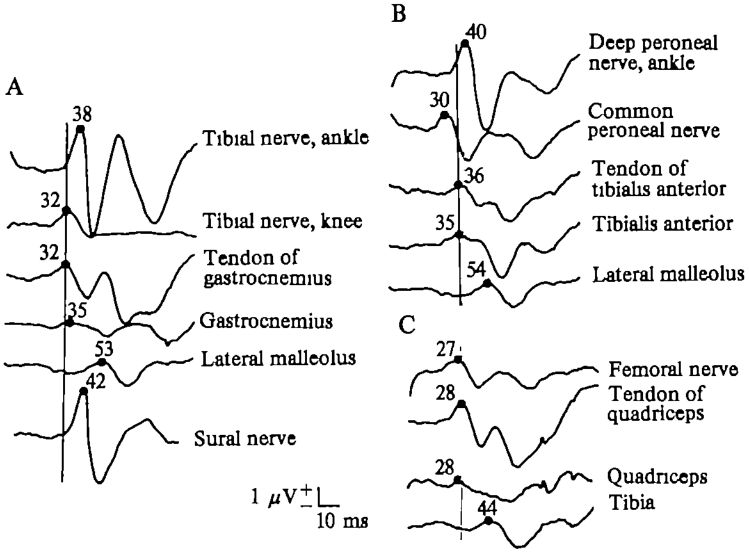

FIG. 9. Grand average of cerebral potentials to mechanical and electrical stimulation at different levels of the leg. A, posterior aspect of the ankle. B, anterior aspect of the ankle. C, knee. The latencies of P1 component to each form of stimulation are indicated over the corresponding peaks. A vertical line has been placed at the P1 latencies evoked by tendon taps at each level.

Stimulation of the posterior sector of the ankle. Fig. 9A contains the grand average of potentials evoked in 8 subjects by the various stimuli to the posterior portion of the ankle. Achilles tap evoked an initial scalp positive component 5.8 ± 1.2 ms before the initial positive component evoked by tibial nerve stimulation at the same level of the ankle ($P < 0.01$) and by 10.4 ± 2.6 ms before the initial positive component evoked by sural nerve stimulation at the same level ($P < 0.01$). This is unexpected since the mechanical stimulation, to be effective, must first be transduced by the skin, tendon and muscle receptors. Yet in spite of this transduction process, the latency to tendon percussion was shorter than to stimulation both of the tibial and the sural nerve at the same level. In fact, the latency of the scalp positivity to Achilles tendon tap was not significantly different from the latency to tibial nerve stimulation at the popliteal fossa, almost 30 cm rostrally, and to tapping on the belly of the triceps surae. These results suggest that percussion of the tendon at the ankle activates receptors proximal to the ankle to account for the shortened latency of its initial evoked potential component recorded from the scalp. In contrast, tapping on the skin overlying the lateral malleolus at the ankle evoked an even later initial positive scalp component (22.4 ± 3.3 ms) indicating that the initial scalp positivity evoked by tendon percussion did not derive from activating cutaneous afferents.

In one subject, Achilles tendon taps evoked the largest amplitude of P1 component at Pz, decreasing in a symmetrical fashion as electrodes were displaced from that site. In contrast, electrical stimulation of tibial and sural nerves evoked the largest amplitudes of P1 component at Pz but showed ipsilateral amplitude enlargement, as reported by Cruse (Cruse *et al.*, 1982) (fig. 10). The latency of the positive component P1 from an Achilles tendon tap at the different electrode locations was within 1 ms of its latency at Cz. Thus the scalp distribution amplitude data indicate that the generators for tibial nerve and Achilles tendon tap SEPs differ. Furthermore, the latency difference is a distinguishing characteristic of these two systems and not a technical limitation due to location of the scalp electrode.

Stimulation of the anterior sector of the ankle. Fig. 9B contains the grand average of potentials evoked by the various stimuli in 8 subjects in the anterior sector of the ankle. Tibialis anterior tendon taps evoked an initial scalp positivity 4.6 ± 2.4 ms before the positive component to anterior tibial nerve stimulation ($P < 0.005$). Again the latency of potentials evoked by tendon taps was not significantly different from that obtained after tapping directly on the tibialis anterior muscle belly (1.0 ± 2.8 ms). Cutaneous tap on the malleolus of the ankle evoked a later first scalp positivity (17.9 ± 4.0 ms) and peroneal nerve stimulation at the head of the fibula an earlier one (5.6 ± 3.2 ms, $P < 0.005$). This latter finding differs from those obtained with the Achilles and quadriceps tendons in which tap stimuli evoked potentials with a similar latency to that observed in stimulation of nerves situated proximally (i.e. tibial nerve at the popliteal fossa and femoral nerve at the inguinal ligament).

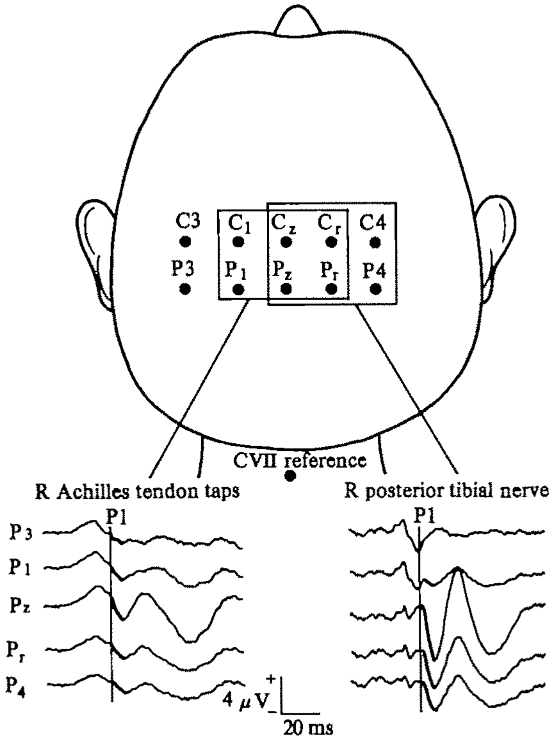

FIG. 10. Scalp distribution of cerebral potentials evoked by stimulating right tibial nerve at ankle and right Achilles tendon tap in one subject. The drawing over the scalp show the electrode positions where the amplitude of P1-N1 component was at least 80 per cent of the amplitude recorded at Cz for each modality. The coronal array of parietal electrodes (P_3, P_1: middle point between P_3 and Pz, Pz, Pr: middle point between Pz and P_4, and P_4) referenced to the skin over the seventh cervical vertebra (CVII) show the different scalp distribution for tibial nerve stimulation (clearly ipsilateral) and Achilles tendon tap (symmetrical) cerebral potentials. Vertical lines were drawn at the peak of the P1 component for each modality. Note that before the P1 component there are additional positive deflections in the scalp recordings reflecting subcortical or spinal components.

Stimulation at the knee. Fig. 9C contains the grand average of potentials evoked by the various stimuli in 8 subjects at the level of the knee. Tapping on the quadriceps tendon evoked an initial positivity 6.2 ± 5.6 ms before electrical stimulation of the tibial nerve at the same level at the popliteal fossa ($P < 0.025$, fig. 9A). There was no significant difference between the latencies to quadriceps tendon stimulation and to electrical stimulation of the femoral nerve 40 to 50 cm proximally at the inguinal ligament. There was no significant difference either between latencies of first positivity to tapping on the belly of the quadriceps muscle and to tapping on the tendon of the quadriceps. Cutaneous stimulation of the tibial tuberosity evoked potentials that occurred later (17.5 ± 4.0 ms).

Relation between Amplitudes of the Scalp Components Obtained to Stimulation of Nerve Trunks and Tendon Taps

There was considerable intersubject variation in the amplitude of the potentials evoked by all forms of stimulation. The standard deviation of amplitudes was usually close to the mean amplitude (*see* Table 1). This variability did not derive from technical considerations such as placement of stimulating electrodes, or transduction of the mechanical stimulus since those individuals with the largest potentials to one form of stimulation usually had the largest potentials to other modes of stimulation (Table 2).

TABLE 2 RANK ORDER* OF THE AMPLITUDE OF THE P1-N1 COMPONENT OF THE CEREBRAL POTENTIALS EVOKED BY ELECTRICAL AND MECHANICAL STIMULATION

Rank order	*Tibial n, ankle*	*Sural n*	*Deep peroneal n, ankle*	*Tibial n, knee*	*Peroneal n*	*Femoral n*	*Tendon of gastrocnemius*	*Tendon of tibialis anterior*	*Tendon of quadriceps*
Ilona	1	1	1	2	1	1	1	1	1
Lisa	2	3	4	—	4	2	2	2	2
Albert	3	2	2	1	6	8	4	6	4
Yao	4	4	3	3	2	3	3	3	7
Dana	5	6	6	5	3	5	6	4	3
Greg	6	5	5	4	5	4	5	5	8
Lee	7	7	7	—	7	6	8	7	5
Seline	8	8	8	—	8	7	7	8	6

*Larger to smaller. — = no potentials obtained because stimulation at motor threshold was painful.

DISCUSSION

The results of this study show that mechanical stimulation of tendons (Achilles tendon, tendon of the tibialis anterior muscle and tendon of the quadriceps) evoke clear scalp potentials that differ in latency from potentials evoked either by stimulation of nerves at the same level in the leg or adjacent cutaneous areas. The latency difference was as much as 23.7 ± 4.0 ms if the measures were taken at the onset of the initial cortical positive component and as much as 31.7 ± 3.1 ms if the peak of the component was chosen. In this study we have emphasized measurement at the peak because of the ease of its definition.

There are several candidate receptors which could be responsible for the generation of tendon tap evoked potentials. Since the mechanical tap of the tendon stimulates the skin, input from cutaneous receptors could be significant. Cutaneous mechanoreceptors are rapidly adapting (velocity or acceleration detectors) or slowly adapting (displacement detectors) (Iggo, 1974). In our experiments, varying the rise time of the mechanical tap indicated that the receptors providing input for the evoked potentials are extremely sensitive to acceleration and therefore are likely to be fast adapting mechanoreceptors. Fast adapting cutaneous mechanoreceptors are pacinian corpuscles such as Golgi-Mazoni and hair follicle receptors. Most of them would be activated by the tap on the tendon through spread of the mechanical vibration to the surrounding skin. It is unlikely that these cutaneous receptors participate in the generation of the first scalp positivity to tendon taps since mechanical stimulation of the skin overlying bones at the same level of the tendons (i.e. lateral malleolus, tibial tuberosity) evoked potentials whose initial positivity occurred more than 20 ms later than those evoked by tendon taps at the same level of the leg.

Tapping on the tendons could also activate receptors in joints lying close to these tendons. Joint capsules contain free nerve endings, pacciniform, Ruffini type and Golgi type corpuscles. Most of their afferent fibres are group II (except those for Golgi type) (Matthews, 1974). Several reasons are against their participation as a source of tendon tap evoked potentials. First, the joints were fixed by a mould, so that very few of these receptors would be activated by the slight mechanical deformation of the tap. Secondly, the conduction velocity of group II afferent fibres would not result in an initial scalp event to mechanical taps at a latency earlier than that to stimulation of the tibial nerve at the same level. Thirdly, in additional studies we found that ischaemia of the foot produced by a pressure cuff placed just above the ankle did not alter the latency of the Achilles tendon evoked potential while the potentials tibial nerve stimulation at the ankle were abolished, similar to the results of Starr *et al.* (1981) using ankle flexion as a means of stretching the muscles to evoke cerebral potentials.

Golgi tendon organs could also be activated by mechanical tendon taps. They are sensitive receptors of muscle tension that are distributed throughout the body musculature with a density nearly as great as that of muscle spindles (Houk *et al.*, 1980). They are situated at the junction between the muscle tendon and extrafusal muscle fibres (Sweet and Eldred, 1960; Bridgman, 1970; Schoultz and Sweet, 1972; Barker, 1974). They are known to have extremely low thresholds in response to active contraction (Jansen and Rudjord, 1964; Houk and Henneman, 1967) and respond poorly to passive stretch (Houk *et al.*, 1971). In man, tendon organ afferents discharge at long latency to muscle stretch, when the muscle reflex contraction first occurs (Burg *et al.*, 1973). If this result also applied to our experiments, Golgi organs would have been activated 35 to 40 ms after the tendon tap, at the time of the first reflex contraction. Since the initial scalp events to tendon taps can be detected 30 to 40 ms after the tendon tap it is unlikely that activation of

Golgi receptors could contribute to this short-latency event. Although Golgi tendon organs can discharge in response to tendon taps, the stretch of a relaxed muscle is a relatively ineffective stimulus and, consequently, they are unlikely to be a significant source of receptor input from the small mechanical deformation of the tendon used in this study.

Receptors in the muscle itself are the most likely source of afferent input for the tendon tap evoked potentials. The primary muscle spindle endings lie midequatorially, in bag and chain fibres (Matthews, 1972). These receptors are extremely sensitive to a rapidly accelerating stretch (Matthews, 1972) and their signals are conducted along fast Ia fibres. Moreover the central pathways for muscle spindle activity project to the cortex through a rapidly conducting system (Phillips *et al.*, 1971; Lucier *et al.*, 1975; Hore *et al.*, 1976). In an earlier study in man, Starr *et al.* (1981) showed that stimulation of a peripheral nerve fascicle, identified as containing muscle spindle afferents, evoked cerebral potentials at short latency.

The secondary muscular endings lie juxta-equatorially, predominantly in the chain fibres on regions that are well striated (Matthews, 1972) and they have a much lower dynamic sensitivity to tendon taps than do primary endings (Lundberg and Winsbury, 1960; Bessou and Laporte, 1962). Moreover, the peripheral conduction velocity of the group II afferent fibres from secondary endings would not permit such an early cortical potential as that obtained to tendon tap stimulation.

Muscle mechanoreceptors like pacciniform corpuscles are found almost exclusively at the musculotendinous junctions, are smaller than pacinian corpuscles (Matthews, 1972) and in the soleus muscle of the cat represent only 2 per cent of the muscle spindles (Barker, 1962). Occasionally a pacinian corpuscle may be found in the muscle. These receptors could be activated by the mechanical disturbance of the tendon but their contribution to the evoked potential is probably very small.

The finding that the potentials evoked by tendon taps occur earlier than on stimulation of the nerve at the same level of the leg could be due to several mechanisms: (1) the distance that the afferent volley must travel to tendon taps is less than that to stimulation of the nerve since the muscle spindle receptors lie proximal to the place of percussion; (2) the peripheral conduction velocity of the afferent nerve fibres from spindles activated by tendon taps is faster than for those activated by percutaneous electrical stimulation of the nerve; (3) the central conduction velocity of the afferent volley to tendon taps may be faster than to electric stimulation of the whole nerve; and (4) a combination of all or some of these possibilities.

The spindle receptors in the triceps surae muscle belly lie 25 to 30 cm proximal to the site of percussion at the ankle which would account for a decrease of 5.6 ms if the fibres conducted at 53 $m \cdot s^{-1}$ (Burke *et al.*, 1981). However, it must also be appreciated that the onset of tendon displacement occurs 1 to 3 ms after activating the vibrator and peak displacement occurs by 10 ms (fig. 1). In addition, there is a time delay involved in the propagation of the percussion wave to activate the spindle receptors (possibly 40–80 $m \cdot s^{-1}$) Brown *et al.*, 1967) and the time for receptor transduction to occur (Burke, 1983). These latter factors would tend to increase the latency of the evoked potentials by 3.5 to 8 ms, whereas the proximal location of the receptors would reduce it by 5 to 6 ms. Using the 3.5 ms figure for time of stimulus transduction and activation of the spindles we estimate that the proximal location of the muscle spindle receptors probably accounts for approximately half (2.5 ms) of the 5.8 ms latency disparity between tendon tap and nerve stimulation at the ankle. The possibility that differences in peripheral conduction velocity from these two methods of stimulation could account for the latency disparity is not supported by recent data derived from epidural recordings in man (Sherwood *et al.*, 1983). In these subjects the latency difference between the potentials evoked by tendon taps and electrical stimulation of the nerves could be accounted for by the proximal location of the receptors activated by tendon taps.

A final possibility to explain latency differences between tendon tap and nerve evoked potentials is that the conduction velocity of the afferent volley to tendon taps is conducted centrally more rapidly than is the volley to electrical stimulation of the whole nerve. Muscle spindle afferents from triceps surae converge on neurons of the dorsal spinocerebellar tract (Lundberg and Oscarsson, 1960; Kröller and Grüsser, 1982) that conduct through the spinal cord quite rapidly in man (65–80 $m \cdot s^{-1}$, Jones *et al.*, 1982), but must synapse in the cerebellum and thalamus before arriving at the cerebral cortex. In contrast, conduction of input from electrical stimulation of mixed nerves to evoke cerebral potentials depends upon the integrity of the posterior columns (Halliday and Wakefield, 1963; Noël and Desmedt, 1975) which are known to conduct relatively slowly (30–50 $m \cdot s^{-1}$, Jones *et al.*, 1982) but have a direct path to the cerebrum with synapses in the gracile and cuneate nuclei and the thalamus. Thus the shorter latencies of the cerebral potentials to tendon taps compared with those evoked by whole nerve stimulation probably reflects a combination of two factors: the proximal location of the receptors activated by tendon tap stimulation coupled with their conduction along a very rapid spinal pathway.

The basis for ipsilateral scalp distribution of tibial and sural nerve SEPs in contrast with the symmetrical scalp distribution of Achilles tendon tap SEPs is not clear. Certainly such results would be compatible with different orientations of their cortical generators. Cutaneous receptors project mainly to areas 1 and 3b and muscle receptors to area 3a to account for the sural nerve and Achilles tendon tap SEP differences (Phillips *et al.*, 1971; Powell and Mountcastle, 1959). Such cortical differences, however, cannot explain the asymmetry between tibial nerve and Achilles tendon tap SEP scalp distributions because both derive from activation of Ia afferent inputs (Burke *et al.*, 1981).

The amplitudes of the potentials evoked by tendon taps were smaller than those obtained to percutaneous electrical stimulation (Table 1). This may be due to the fewer number of nerve fibres activated by stretching the muscle, as well as their relative asynchrony compared with electrical stimulation of the entire nerve. Individuals with the largest potentials to one form of stimulation usually had the largest potentials to other modes of stimulation. While it is possible that the number of central neurons and tracts activated by the same stimulus can differ in different subjects it is more likely that there are individual anatomical differences in the cortical dipole orientations similar to those described for the scalp distribution of somatosensory or visual evoked potentials (Halliday, 1982; Seyel *et al.*, 1983). Another possibility is that there are individual differences in the resistive-capacitative properties of the medium between the cortical generators and the surface recording electrodes, resulting in different filtering properties of the volume conductor.

Clinical and Physiological Significance

Somatosensory potentials evoked by electrical stimulation of peripheral nerve trunks and recorded from scalp electrodes are now an accepted diagnostic procedure (Halliday, 1978; Starr, 1978). Potentials evoked by natural activation of somatosensory pathways through cutaneous mechanoreceptors (Pratt *et al.*, 1979*c*), skin cooling (Chatt and Kenshalo, 1979), noxious thermal stimulation (Carmon *et al.*, 1978) and muscle stretch (Starr *et al.*, 1981) have also been described but thus far have not had clinical applications. This study shows that mechanical stimulation of tendons (Achilles tendon, tendon of the tibialis anterior muscle, tendon of the quadriceps) evoked cerebral potentials that most probably reflect activation of a fast somatosensory pathway originating in muscle spindles and group I fibres. Long-latency muscle reflexes of triceps surae may be demonstrated in humans to abrupt muscle stretch (Berardelli *et al.*, 1982). Abnormalities of long-latency reflexes have been reported in reflex myoclonus (Dawson, 1947; Halliday, 1967; Chadwick *et al.*, 1977; Shibasaki *et al.*, 1978) and parkinsonian rigidity (Tatton and Lee, 1975), but there is no agreement as to the mechanisms responsible for their generation (Marsden *et al.*, 1983). Moreover, it is thought that long-latency reflexes appearing in different muscles may have different origins (Marsden *et al.*, 1983). The simultaneous study of muscle reflexes and muscle stretch evoked potentials might provide additional information as to mechanisms underlying long-latency muscle reflexes and the physiology of motor systems in health and disease. Furthermore, the use of a physiological stimulus such as muscle stretch that tests the transmission in neural pathways under conditions more closely resembling the natural states is, theoretically, more likely to demonstrate functionally important deficits.

ACKNOWLEDGEMENTS

This study was supported in part by grant NS11876 from the National Institutes of Health. L.C. was supported in part by a scholarship from The Rotary Foundation of Rotary International.

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(*Received May 11, 1984. Revised July 31, 1984. Accepted August 7, 1984*)

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SPATIOTEMPORAL RESPONSES OF THE VISUAL SYSTEM IN DEMYELINATING DISEASES

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SUMMARY

Previous studies have shown that, in patients with lesions of the visual pathway, contrast sensitivity (CS) measured with stationary sine-wave gratings can demonstrate deficits, that is, anomalies in pattern detection. The purpose of this study was to investigate whether temporal processing can be affected in demyelinating lesions of the visual pathway. CS was measured for eight spatial frequencies (SF), using stationary and temporally modulated stimuli in a group of 10 patients with multiple sclerosis or optic neuritis. A control group was composed of 48 normal eyes. With stationary stimuli, CS losses were found in 17 eyes of patients; 11 of these eyes were 'unaffected'. The importance of the CS measurements in detecting early subclinical visual damage is emphasized. The effect of temporal modulation in patients with CS deficits was different from that observed in normals: CS deficits were modified by temporal variation in three distinct manners. In 7 eyes (type 1 effect), temporal modulation reduced the deficit at all SFs. In type 2 (5 eyes), the effect was reversed at low and high SFs: the deficit was reduced at low SFs (below 2–3 cycles/deg) and aggravated at high SFs. In type 3 (4 eyes), CS deficit was aggravated over most SFs. Thus these patients exhibited anomalies of the spatiotemporal responses which could not be predicted by the CS to stationary stimuli. Some theoretical models of spatiotemporal processing proposed in normal vision might account for our results. Possible explanations of these findings are proposed and discussed.

INTRODUCTION

Spatial processing in human vision has been studied by a number of investigators (*see* Campbell and Green, 1965; Robson, 1966; Campbell and Robson, 1968). The method typically employed tests an observer's ability to detect sine-wave gratings of different spatial frequencies. The resultant contrast sensitivity function in normal observers has been shown to exhibit a characteristic shape, with an attenuation of contrast sensitivity (CS) at low and high spatial frequencies (SF) and a maximum between 2 and 5 cycles/deg.

Recently the CS function of patients with multiple sclerosis (MS), optic neuritis

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(ON) and other diseases involving the visual pathway has been studied in several investigations (*see* Bodis-Wollner and Diamond, 1976; Regan *et al.*, 1977; Zimmern *et al.*, 1979). All these studies, in which stationary gratings were used as stimuli, have shown that demyelination of the visual pathway can alter the shape of the CS function. These findings were interpreted as malfunctions of the neural channels selective to spatial frequency, the channels which have been proposed as the mechanisms responsible for the analysis of spatial information in normal human vision (Campbell and Kulikowski, 1966; Blakemore and Campbell, 1969; Sachs *et al.*, 1971).

Spatiotemporal processing has also been extensively studied in human vision (*see* Robson, 1966; Kelly, 1966; Pantle, 1971; Koenderink and Van Doorn, 1979). It has been shown that temporal variations of the sine-wave grating stimulus alters the spatial CS function. These changes are dependent on the spatial frequency region; for example, the fall-off in sensitivity at low SFs is retained only when the temporal frequency (TF) is also low (up to 5–6 Hz), but a TF of 15 Hz abolishes the fall-off (Robson, 1966). Temporal modulation does not change the form of the fall-off at high SFs, but tends to reduce the sensitivity. The models proposed to account for spatiotemporal processing agree in general terms that there are two functionally different neural channels, one of which analyses temporal variations and the other spatial variations in contrast (Keesey, 1972; Kulikowski and Tolhurst, 1973; Tolhurst, 1973; Wilson and Bergen, 1979). In a recent treatment of spatiotemporal processing, two temporal channels, one sensitive to low, the other to high temporal frequencies were proposed (Watson and Robson, 1981).

In pathological conditions, such as demyelination of the visual pathway, which can alter pattern detection, it is not known whether temporal processing can be affected as well. Hess and Plant (1983) determined the effect of temporal modulation on CS deficits in patients with optic neuritis. They used gratings of 0.5 and 4 cycles/deg and found that for 4 cycles/deg gratings no change in the CS deficit occurred at any temporal frequency. In contrast, the deficit tended to decrease with increase in TF for gratings of 0.5 cycles/deg.

In our present study, we compared the effect of temporal variation of the stimulus on CS in normal observers and in patients (MS and ON) with CS losses. This was done by measuring the sensitivity to stationary and temporally sinusoidally modulated stimuli of a wide range of SF. These experiments were conducted primarily to determine whether spatiotemporal responses is these patients would show abnormalities other than those demonstrated by the usual CS to stationary stimuli and whether these effects would be consistent with the psychophysical models mentioned above.

Another issue, of clinical importance, is the diagnostic value of CS measurements. In the study reported by Zimmern *et al.* (1979) on patients with ON, CS tests verified the abnormalities found with neuro-ophthalmological examination. Regan *et al.* (1977) reported that CS tests confirmed a visual damage suspected on the basis of some subjective complaint in MS patients. In order to investigate whether CS measurements can reveal subclinical damage without any (subjective or objective) clinical manifestation, we studied the affected as well as the nonaffected eyes of all our patients.

METHODS

Apparatus

The stimuli consisted of vertically orientated, stationary or sinusoidally countermodulated sine-wave gratings. They were generated on a Cambridge video display by conventional means (Schade, 1956; Campbell and Green, 1965; Campbell and Robson, 1968) and controlled by a Nascom microcomputer. A frame rate of 100 Hz was used. Contrast was measured to be linear up to 60 per cent, for all SFs and TFs that were used, including the highest ones. All stimuli were presented at a mean luminance of 60 cd/m^2.

The display screen subtended a visual angle of 7.5 deg vertically and 9.4 deg horizontally and was surrounded by a grey field. The surround has a luminance close to the mean luminance of the pattern and subtended a visual angle of about 27.5 deg horizontally and vertically.

The viewing distance was set at 150 cm and held constant by means of a chin rest. Subjects were instructed to fixate on the centre of the screen. The fixation area was marked by four thin lines positioned orthogonally, which circumscribed a free central area of 2 deg. This type of fixation was preferred to a fixation point on the centre of the screen, which might interfere with the detection of spatial pattern.

Each eye was tested separately. The nontested eye was occluded by a translucent eye patch. This arrangement prevented test field 'blackening', a sensation due to binocular rivalry when one eye is occluded by an opaque patch. The room lights were baffled but left on during the testing. The ambient light level was about 52 cd/m^2.

Test Procedure

Contrast thresholds were obtained on all subjects with SFs of 0.5, 1, 2, 3, 4, 6, 8 and 12 cycles/deg, stationary and countermodulating at rates of 1, 5 or 15 Hz

All subjects wore their best correction.

A variation of the von Bekesy method of tracking, as applied by Wetherill and Levitt (1965), with three ascending and three descending sequences, was used to measure the thresholds. Each stimulus was initially presented at a contrast which was clearly visible. Thresholds were then determined by the subject who reduced the contrast by pressing a hand-held button until he could no longer see the grating, then increased it until some form of stimulus could just be detected on the screen. The procedure was repeated until the contrast had reversed six times. The mean of the last four contrast reversals was taken as the threshold for each SF. This procedure was conducted under computer control.

In each series of measurements the spatial and temporal frequencies were chosen in pseudo-randomized order.

Control Subjects

Twenty-six normal subjects whose ages ranged from 22 to 60 years took part in the experiment. Thus 52 eyes were initially tested. The CS function, for stationary gratings, of each control eye was compared to the mean CS function of the remaining 51 eyes. Four eyes were eliminated from the control group because of strong astigmatism or myopia that could not be corrected completely. All the remaining eyes were retained as controls. Their Snellen visual acuities, measured with refractive correction where necessary, were 20/25 or better.

Employing a larger number of controls enabled us to make quantitative estimations of the variability of these data. Unless otherwise stated, in all analyses of the normal data presented in the results section, 'normal limits' refer to the 99 per cent confidence intervals which where calculated, for each point, by adjusting the standard error across the eight spatial frequencies (Hays, 1973).

Patients

The patient group was composed of 5 males and 5 females whose ages ranged from 17 to 51 years. There were two subgroups. In the first subgroup, 5 patients had a history of isolated ON. The ON was unilateral in 4 cases and affected both eyes in 1 case. One patient of this subgroup developed other signs of MS after the CS test and was diagnosed as probable MS. The second subgroup comprised 5 patients. Four of them were diagnosed as definite MS and 1 as possible MS according to the scale defined by Rose *et al.* (1976). Among them, 3 had a history of ON in one eye while 2 (Cases 7 and 10) had no clinical evidence of visual involvement in either eye.

A total of 9 affected eyes had, at the time of testing, all recovered from the acute episode of ON in that the visual acuity was 20/25 or better in 5 of the eyes. The remaining 4 eyes had a visual acuity of 20/40, 20/50, 20/50 and 20/70 respectively. Three patients (Cases 5, 6 and 8) had, in their affected eye, a residual scotoma from the ON. However, at the last examination (performed shortly before the experiments) the scotoma was tiny, especially in Cases 5 and 6, and all 3 patients were able to see without difficulty the fixation target at a distance of 150 cm. Some of these patients still complained of some subjective visual disturbance in the affected eye as compared with the unaffected eye. All 11 unaffected eyes had a visual acuity of 20/25 or better.

All patients had a systematic neuro-ophthalmological investigation before being tested. Visual acuity was assessed by the use of Snellen charts. The optic discs were examined and photographs of the fundi were taken; the visual fields were measured and afferent pupillary defects (Marcus-Gunn pupil) were noted when present. Patients were selected so that none of them presented any oculomotor dysfunction. Visual evoked responses were obtained by alternating checkerboard patterns. The results of the tests are shown in the Table.

RESULTS

Results from Normals

The CS function of 48 control eyes were obtained and a mean control curve with 99 per cent confidence limits was derived for each of stationary and 1, 5 and 15 Hz countermodulated stimuli (fig. 1).

Spatiotemporal modulation transfer functions published earlier (*see* Kelly, 1966; Robson, 1966) were derived from small numbers of experienced observers. Our results, from a large group of inexperienced subjects, show the same characteristic effect of temporal variation on CS as those reported in the literature. As expected (fig. 1), the high-frequency attenuation occurs at all TF, whereas the low-frequency fall-off occurs only with low TF (1 Hz) and is completely abolished with 15 Hz.

The changes in CS with temporal variation were further examined by calculating the ratio of the CS obtained with temporally modulated stimuli to the CS obtained with the stationary gratings at each SF. These ratios are represented in fig. 2 for each of 1 Hz (triangles), 5 Hz (squares) and 15 Hz (circles). The horizontal reference line (asterisks and solid line) represents a ratio of one that would have been obtained if no change in CS with temporal modulation had occurred. Curves were examined by repeated measures analysis of variance in polynomial trend which indicated that the quadratic form of the CS function was significantly altered by temporal modulation ($P < 0.01$). As can be seen in fig. 2, the reduction in sensitivity for gratings with SFs above 2 cycles/deg is more pronounced at higher TFs. For 1 and 2 cycles/deg gratings, sensitivity is reduced with 1 and 15 Hz. At SFs below 1 cycle/deg sensitivity is higher with temporal modulation, at any TF.

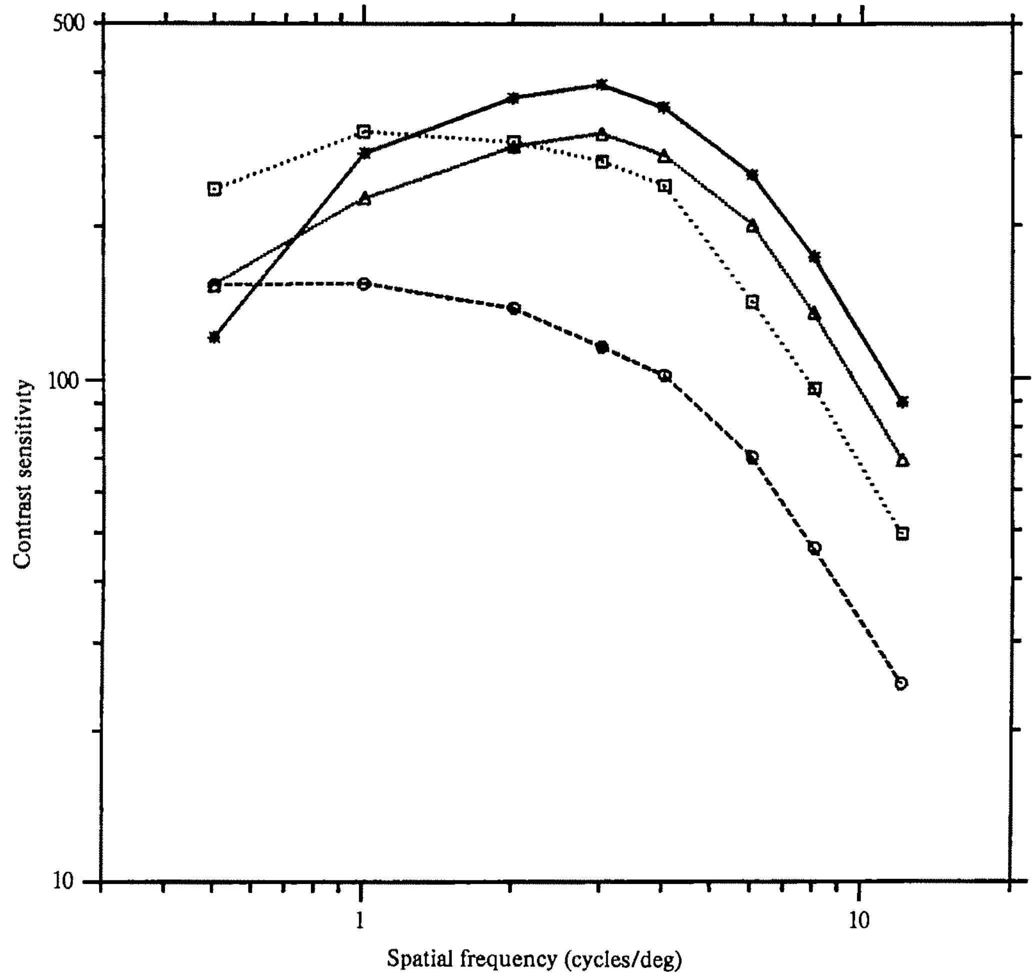

FIG. 1. Mean contrast sensitivity functions for 48 normal eyes. Sensitivity, as the reciprocal of contrast threshold (ordinates) is plotted as a function of spatial frequency (abcissae). CS functions under the four different conditions are represented: for stationary gratings (asterisks, solid lines); 1 Hz (triangles); 5 Hz (squares) and 15 Hz countermodulated gratings (circles).

Results from Patients

The CS function of each of the patients' eyes was individually compared with the mean control function. In all 9 affected eyes, that is with a history of ON (*see* Table), a CS deficit was found despite the clinical recovery. One patient in this group (Case 4, aged 17 years), who presented with bilateral ON at the age of 7 years, complained of subjective visual disturbances such as inability to distinguish different shades or difficulties in reading. VERs did not show any abnormality while a CS loss was

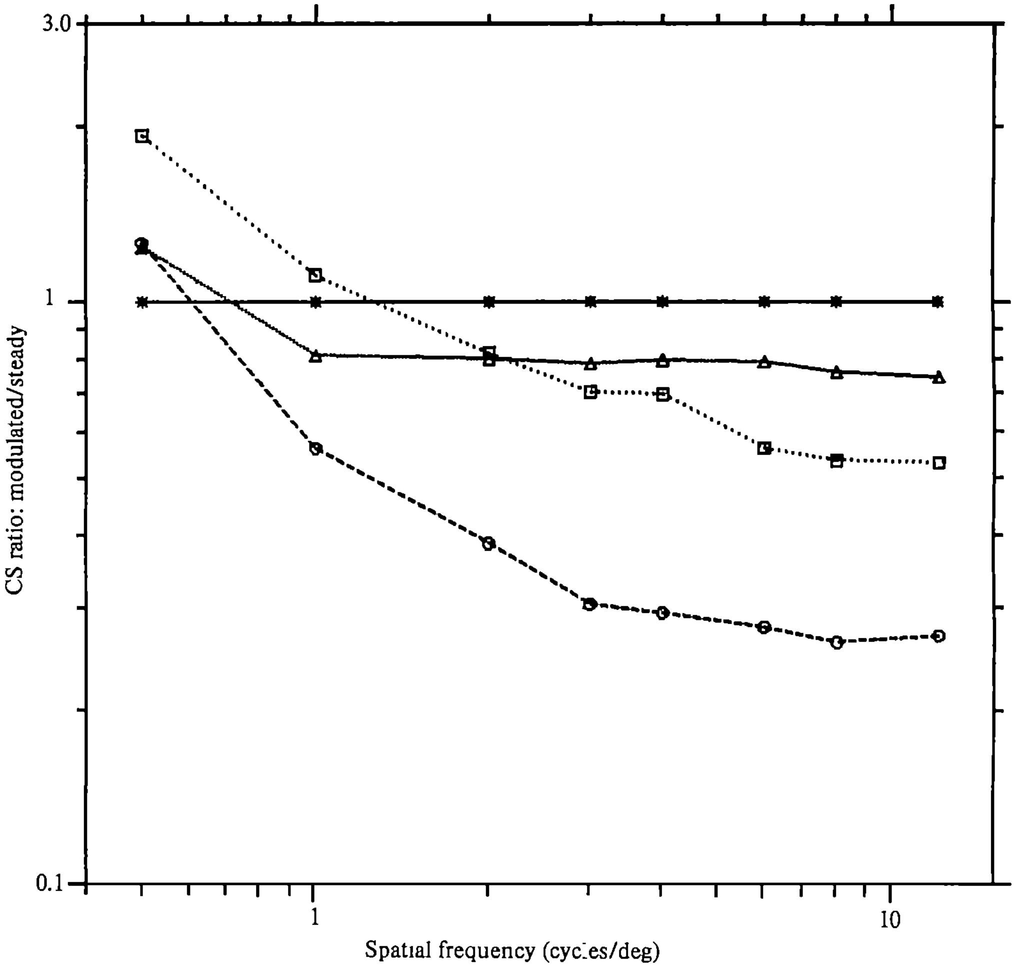

FIG. 2. The effect of temporal variation of stimuli on the visual sensitivity in normals. The difference between sensitivities to a temporally modulated and a stationary grating, expressed as a ratio (ordinates) *versus* spatial frequency (abcissae) is plotted for each temporal frequency of the grating 1 Hz (triangles), 5 Hz (squares) and 15 Hz (circles). The horizontal line at Y = 1 (asterisks, solid line) represent the similar plot for 0 Hz (ratio = 1)

found in both eyes. Out of 11 unaffected eyes, 8 presented a CS loss despite a visual acuity of 20/25 or better. Among these, 2 eyes (Cases 7-R and 8-R) had no abnormality of the VERs. VERs were defined as 'delayed' (*see* Table) when the latency of P1 was increased and as 'abnormal' when the amplitude of the potentials was reduced.

Visuograms of patients were derived by plotting, at each SF, the ratio of the patient's CS to the mean CS of normals, for stationary and each of the countermodulated gratings.

TABLE RESULTS OF NEURO-OPHTHALMIC INVESTIGATIONS IN PATIENTS

Case	*Sex*	*Age*	*Diagnosis*	*Eyes*	*Afferent pupillary defect*	*Optic discs*	*Visual field*	*Visual acuity*	*VERs*	*CS function*
1 (M H)	M	31	Unilat	R UA	No	Normal	Intact	20/15	—	Selective loss*
			ON	L ON	MG 1/2+	Normal	Intact	20/15	—	Generalized loss*
2 (C B)	F	39	Unilat	R ON	MG 2+	Pallor	Intact	20/20	Delayed*	Generalized loss
			ON	L UA	No	Normal	Intact	20/15	Normal	No loss
3 (K D)	M	23	Unilat	R UA	No	Normal	Intact	20/15	Normal	No loss
			ON	L ON	Trace MG	Pallor	Intact	20/20	Delayed	Generalized loss
4 (M O)	F	17	Bilat	R ON	No	Pallor	Intact	20/50	Normal	Generalized loss
			ON	R ON	No	Pallor	Intact	20/50	Normal	Nonselect loss
5 (L S)	F	25	MS	R UA	No	Normal	Intact	20/15	—	Generalized loss
			(probable)	L ON	No	Pallor	Scotoma	20/20	—	Nonselect loss
6 (P R)	M	42	MS	R UA	No	Pallor	Intact	20/20	Abnormal*	Nonselect loss
			(definite)	L ON	MG	Pallor	Scotoma	20/40	Abnormal'	Generalized loss
7 (G E)	F	34	MS	R UA	No	Normal	Intact	20/25	Normal	Generalized loss
			(definite)	L UA	No	Normal	Intact	20/25	Delayed	Generalized loss
8 (R A)	M	51	MS	R UA	No	Pallor	Intact	20/25	Normal	Generalized loss
			(definite)	L ON	No	Pallor	Scotoma	20/70	Abnormal	Generalized loss
9 (S O)	M	35	MS	R UA	No	Normal	Intact	20/15	Delayed	Selective loss
			(definite)	L ON	No	Normal	Intact	20/15	Delayed	Selective loss
10 (B B)	F	24	MS	R UA	No	Normal	Intact	20/20	Delayed	Selective loss
			(possible)	L UA	No	Normal	Intact	20/20	Normal	No loss

MS = Multiple sclerosis ON = optic neuritis UA = unaffected MG = Marcus-Gunn pupil R = right eye L = left eye VERs = visual evoked responses CS = contrast sensitivity * For explanation of 'delayed' and 'abnormal' VERs and 'selective' and 'generalized' CS loss, *see* text

Visuograms for stationary stimuli showed different types of CS losses. Some typical examples are shown in fig. 3A–D. In these figures, the visuograms represent the difference between the data from the patient's eye and the control curve and are compared to a reference line denoted by squares. The reference line was obtained by calculating the ratio of the sensitivity of each control's eye to the mean sensitivity, as was done for the patients. The mean of the 48 ratios (horizontal reference line) and the 99 per cent confidence intervals (vertical bars) were derived. In this figure, the magnitude of the loss increases downwards.

The most frequent type of deficit, observed in 13 cases, was a deficit affecting all the SFs tested (fig. 3A, B). These deficits are referred to as 'generalized' losses. In 6 cases, the magnitude of the loss increased as a function of SF; two examples, Cases 1-L and 8-L, are shown in fig. 3A. In 3 cases, although the loss affected all SFs, its magnitude was slightly larger at medium or low SF regions. Finally, 4 of the 13 cases demonstrated a nonselective loss, that is of about the same magnitude over all the SF range (two examples are represented: 5-L, 6-R, fig. 3B).

Losses that could be classified as selective were less frequent (4 cases). The loss affected selectively the low-frequency region in one case (1-R, fig. 3C) and high SFs in another (9-L, fig. 3C). A notch-like deficit (9-R, fig. 5D), affecting SFs of 2 and 3 cycles/deg more than the others, was observed in 1 case. Finally, in another eye, the loss affected both the lowest SFs (0.5 and 2 cycles/deg) and the highest (8 and 12 cycles/deg); this example is not shown. No one type of loss was specific to MS or ON.

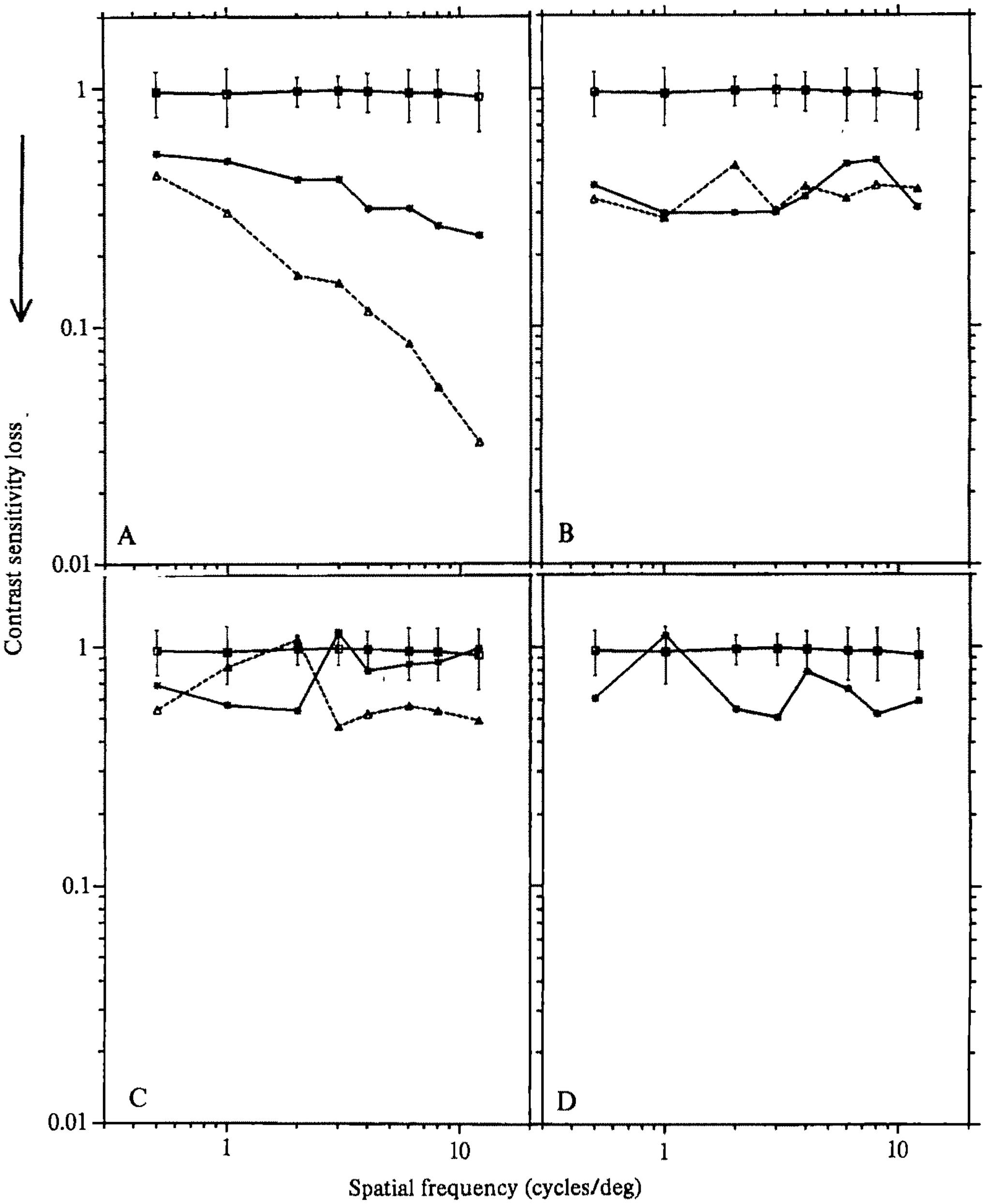

FIG. 3. Different types of contrast sensitivity deficits observed in patients, with stationary stimuli exclusively Visuograms, expressed as ratio of sensitivities of patient and mean of normals (ordinates) as a function of spatial frequency (abcissae). The continuous line (squares) has been obtained by calculating the ratio of the sensitivity of each control eye to the mean sensitivity (as for patients) and deriving the mean of 48 control ratios. The vertical bars indicate 99 per cent confidence limits of the mean ratio A and B give examples of CS losses affecting all the SFs A, the magnitude of the loss increased with SF (Case 1-L, asterisks, 8-L, triangles) B, CS loss was slightly more pronounced at medium-low SFs (5-L), or of about the same magnitude over the SF range (6-R). C, low-frequency selective loss (1-R) and a high-frequency selective one (9-L). D, notch-like deficit (9-R) affecting 2 and 3 cycles/deg more than others. Note that CS loss increases downwards since the quality actually plotted is the CS ratio

One of the primary purposes of this study was to investigate the effects of temporal variation on the sensitivity deficits of patients as found with the CS function for stationary stimuli. Thus, for each eye, visuograms for 1, 5 and 15 Hz were derived by the same method as for stationary visuograms, that is the ratio of the patient's CS for a particular TF to the mean CS of controls for the same TF were calculated. For the sake of comparison, all visuograms (0, 1, 5 and 15 Hz) were plotted in the same graphs (fig. 4). The horizontal reference line and the error of the mean ratio (represented by vertical bars) were calculated as for fig. 3 and refer to the steady visuograms only. However, normal limits were calculated in the same way for 1, 5 and 15 Hz, respectively and the visuograms at each TF were compared to the corresponding normal limits, which are not represented in this figure.

It was found that temporal variation of the stimuli may have various effects on the CS losses observed with stationary stimuli. Fig. 4 shows examples of several types of effects. The four visuograms of each example are represented with 0 Hz (asterisks and solid lines), 1 Hz (triangles), 5 Hz (squares) and 15 Hz (circles). The original CS functions of each patient given as examples in fig. 4 are shown in fig. 5 for the four different conditions. According to the effect of temporal variation observed, the eyes tested were classified into three distinct types.

Type 1 effect was observed in 7 cases (fig. 4A, B). Introduction of temporal modulation produced less of a loss at all SFs when compared to the loss evidenced by the use of steady targets, that is temporal variation reduced the loss; the most improvement was observed with 5 Hz in most cases. Two typical examples are shown (Cases 3-L, 8-L, fig. 4A). Another example in which CS returned to normal limits at a number of SFs when 5 and 15 Hz were used is shown in fig. 4B (Case 5-R). This effect (type 1) was generally more pronounced at low or medium SFs. Moreover, all TFs improved the CS except in one case, shown in figure 4B (6-L), in which 15 Hz aggravated the loss whereas 5 Hz improved it.

In type 2 (fig. 4C), observed in 5 cases, the effect of temporal variation was dependent on SF. At low frequencies, below 2 or 3 cycles/deg, the deficit was reduced and the best effect was produced by either 5 or 15 Hz while at high SFs, the deficit was aggravated and the worst effect was produced by 1 Hz in all cases (for example, Case 5-L, fig. 4C). The deficit remained unchanged at SFs between 2 and 4 cycles/deg.

In type 3 effect, observed in 4 cases, temporal variation aggravated the deficit over most of the SF range and with all TFs. One example, Case 7-L, is shown (fig. 4D, lower part). In another case (not shown in fig. 4) a selective high-frequency loss observed with stationary gratings changed to a nonselective deficit when 1 Hz was used (9-L, fig. 5H).

Finally, another type of effect was observed in one case only (9-R) in which a notch-like deficit was observed to stationary stimuli. Temporal variation improved the sensitivity selectively at those SFs affected by the deficit, that is, 2 and 3 cycles/deg, 'repairing' the notch (fig. 4D, upper part).

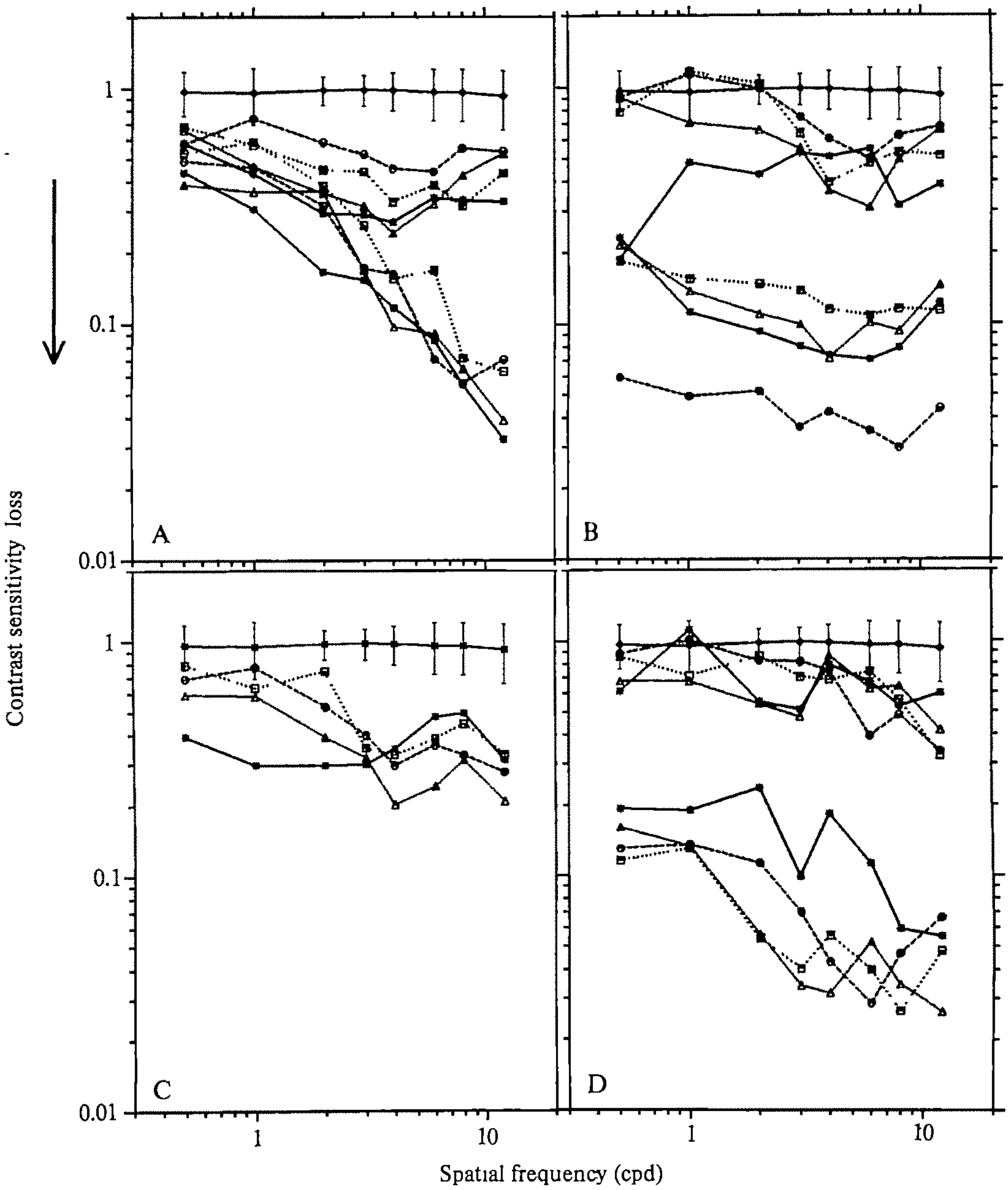

FIG. 4. Effect of temporal variation on CS deficits in patients (typical examples). All figures illustrate visuograms, i.e. ratio of sensitivities of patient and normals (ordinates) as a function of SF (abcissae) For each example, visuograms with 0 Hz gratings (asterisks, solid line), 1 Hz (triangles), 5 Hz (squares) and 15 Hz (circles) are represented. The reference line at Y = 1 and the vertical bars are the same as in fig. 3, referring to visuograms with stationary gratings only. The similar reference limits for 1, 5 and 15 Hz, to which 1, 5 and 15 Hz visuograms have been compared, are not shown A, type 1 effect. All rates of temporal variation reduced the deficit (Case 8-L, lower part; 3-L, lower part). B, two particular examples of type 1 effect. In 5-R (upper part) CS returned to normal limits at medium-low SFs when temporally modulated stimuli were used. In 6-L (lower part), 1 and 5 Hz reduced the deficit, only 15 Hz aggravated it. C, type 2 effect (5-L). Temporal variation reduced the deficit at low SFs and aggravated it at high SFs. D, type 3 effect (7-L, lower part). All TFs aggravated the deficit. With 9-R (upper part of figure), a notch-like deficit was observed with stationary gratings; the 'notch' disappeared when temporal variation was introduced.

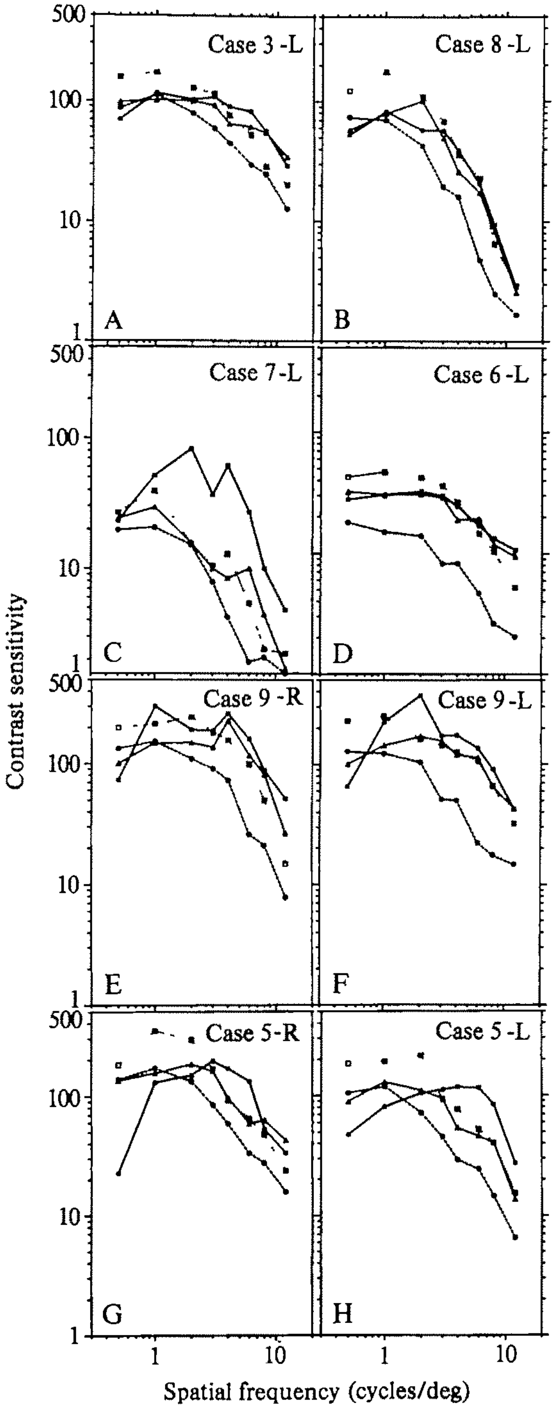

FIG. 5. CS functions of patients eyes of whom visuograms are represented in fig. 4. All four TFs are represented: symbols used are the same as in fig 4

It has to be noted that, in 3 patients, the same type of effect of temporal modulation was observed in both eyes. In all others, right and left eye exhibited different types of this effect.

In the only 3 unaffected eyes in which no CS deficit was found, the effect of temporal variation on the stationary CS function was similar to that observed in the normal subjects.

DISCUSSION

Study of the CS function with stationary stimuli in our group of patients showed a CS deficit in all of the 9 affected eyes and in 8 out of the 11 unaffected eyes. Among the 8 unaffected eyes in which a CS loss was demonstrated, visual evoked responses were studied in 6. VERs were abnormal in 3 eyes and equivocal in one eye; however, the VERs did not show any abnormality in 2 eyes despite a definite loss in CS. These results lead to the conclusion that CS measurements can demonstrate some residual visual loss resulting from an acute episode of ON despite a good visual acuity. More importantly, CS test can reveal a subclinical visual damage in eyes with no objective nor subjective clinical manifestation even when, in some cases, the VERs show no abnormality. In addition, the study emphasizes the necessity for comparison of patients to a group of normal controls rather than using the contralateral 'unaffected' eye as a reliable control.

In an as yet unpublished study of normal subjects for an influence of age on CS, a reduction in CS was found in subjects over 30 years of age as compared with subjects below 30 years. This age-dependent reduction affected all SFs and was statistically significant. In order to eliminate, in patients over 30 years, an age factor as an eventual cause of the CS deficit, CS function of each patient over 30 was also individually compared to a mean CS function derived from normal subjects over 30. Using this procedure, all patients were still shown to present a CS loss. We therefore concluded that, although significant, the age-dependent reduction in CS observed in normals could not account for any of the CS losses found in our patients.

From the study of the CS function using steady and temporally modulated stimuli in patients, the results from the 3 eyes with no CS loss showed that the effect of temporal modulation on CS was similar to that observed in normal subjects. In the 17 eyes of patients with CS deficits, our chief findings were that temporal variation altered the CS in a different way than that observed in normals. When temporal modulation was introduced, the CS deficits were modified in three distinct manners. According to the effect observed, the eyes tested were classified into the following types. In type 1 (7 eyes), the deficit was reduced over most SFs, and in general with all TFs, although more markedly at the medium and low SFs and with higher TFs. In type 2 (5 eyes), CS deficit was reduced by temporal modulation at low SFs (below either 2 or 3 cycles/deg) and aggravated at high SFs. In type 3 (4 eyes), CS deficit was aggravated over most SFs and with all TFs. In 1 case, of type 3 effect, a loss which formerly confined to high SFs was extended to all SFs when temporal modulation was introduced. Finally, in 1 case with a 'notch' deficit, CS was improved selectively at those SFs affected by the loss, that is, the 'notch' disappeared with temporal modulation.

Only one other similar study has been reported (Hess and Plant, 1983) on the effect of temporal variation on CS deficits. In this study, on 8 patients with unilateral optic neuritis, it was found that at low SF (0.5 cycles/deg), the deficit decreased with increase in TF, whereas no effect was observed at high SF (4 cycles/deg). This effect is the same as type 2 effect that we describe on a wider range of SFs, and probably also similar to a number of those cases that we have classified as type 1 effect. The comparison, however, is rendered difficult by the fact that deficits were defined differently in both studies.

Before speculating about possible implications of these findings, the mechanisms proposed for spatiotemporal processing in normal vision are briefly discussed. There is a body of psychophysical data which has been interpreted as evidence of the existence of two sets of detectors, one selective for spatial and the other for temporal variations in luminance (Keesey, 1972; Kulikowski and Tolhurst, 1973; Tolhurst, 1973). Because there is rough similarity between response characteristics of these psychophysical channels and the response of the X and Y cells described in the cat retina (Enroth-Cugell and Robson, 1966; Cleland *et al.*, 1979), these two systems have been labelled, respectively, sustained (X) and transient (Y) channels. The sustained channel is more sensitive to spatial attributes of the stimulus. The transient channel is more responsive to temporal attributes of the stimulus, but it is generally thought to be more sensitive to low than to high SFs (Kulikowski and Tolhurst, 1973; Breitmeyer *et al.*, 1981). Recently, Watson and Robson (1981) have proposed two distinct hypothetical sets of detectors, one selective for low, the other for high TFs, respectively. Their similarity with the sustained and transient systems was pointed out. Most importantly, they have demonstrated that the high TF system (transient) can provide enough spatial information to permit discriminations between at least three spatial patterns although it is much poorer at spatial discrimination than is the low TF system (sustained).

The results from the patients appear to give additional evidence to some of these assumed properties of the sustained and transient channels. Indeed, in patients of type 1 effect of temporal variation, pattern detection, which was deficient when targets were steady, was notably improved when stimuli were temporally modulated; and this was observed at all SFs. Moreover, the high TFs improved pattern detection better than low TF. It might be speculated that this group represents a condition in which the sustained channel is deficient whereas the transient channel is spared by the lesion. The improvement of spatial analysis (at all SFs) with rapidly modulated stimuli would imply that the transient system is capable of providing spatial information; moreover, the coarse type of spatial analysis that this system allows in normal vision might be used to improve form analysis when the sustained channel is deficient. The one case described with a notch-like deficit was selectively improved with rapidly modulated stimuli (5 and

15 Hz) and can be included in this first group if it is assumed that the transient system is not affected and would be used to compensate for the poorly detected spatial targets.

In patients of type 3 effect, pattern detection was deficient when the targets were stationary and even more deficient with temporally modulated stimuli at all SFs. We suggest that these cases might represent a condition in which low and high TF mechanisms are affected to different degrees. Assuming this hypothesis is true, there is no correlation between the relative deficiency of the two TF mechanisms in the two eyes of the same patient. Moreover, each of these two mechanisms can be affected equally over the SF range or unequally at high and low SF regions. In addition, this group may also be suggested to present the same condition as described in previous studies of MS patients in whom critical flicker frequencies were found to be reduced (Parsons and Miller, 1957; Titcombe and Willison, 1961).

Finally, in type 2 effect, pattern detection was deficient with stationary gratings. With temporal variation two opposite effects were observed at high and low SFs. At low SFs, spatial resolution was improved with rapidly modulated stimuli; at high SFs, it was slightly worsened. One possible explanation is that, in this group, only the low TF channel is deficient while the unaffected high TF mechanism is capable of compensating for deficiencies in spatial analysis only at low SFs. At high SFs, this system would not be sufficient for pattern analysis; the slight worsening effect observed with high TF reflects the usual effect of temporal modulation on CS at the high SFs.

In conclusion, study of the CS function using stationary stimuli in patients with MS or ON is a sensitive test which can provide evidence for subclinical lesions of the visual pathway. Study of the temporal CS functions can show functional abnormalities which cannot be predicted by the CS function to stationary stimuli. Our results can be interpreted as supporting the findings of previous psychophysical studies in normals, that is on the existence of two functionally separate channels with different spatiotemporal response properties. A demyelinating lesion of the visual pathway might affect each of these systems separately or both of them to unequal degrees in different patients and in different eyes of the same patient.

ACKNOWLEDGEMENTS

We are very grateful to Drs R. E. Appen and H. S. Schutta for allowing us to study their patients, and to Dr R. E. Appen for supplying neuro-ophthalmological assessments. VERs and clinical tests were kindly supplied by the Departments of Neurology and Ophthalmology, University of Wisconsin Hospitals, Madison. We thank Drs T. C. T. Yin and P. H. Smith for critical comments on an earlier draft of this paper; Dr J. N. Verhoeve for valuable assistance in statistical analysis and comments on the manuscripts; Dr D. O. Bowker and R. K. Kochhar for assistance with computer programing, Professor C. Geronimi for discussion and T. P. Stewart for photographic assistance. We also thank all patients and control subjects who took part in this study.

The first author was supported by a grant from the Algerian Ministry of Education and Research. This study was partly supported by the Wisconsin Center on Mental Retardation-Core support grant

HD 03352, and an unrestricted fund for research to prevent blindness awarded to the Ophthalmology Department.

Informed consent was obtained from all patients and control subjects (Declaration of Helsinki, *British Medical Journal*, 1962, **2**, 177).

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(*Received March 20, 1984. Revised July 3, 1984. Accepted August 7, 1984*)

Brain (1985), **108**, 139–152

MEMBRANE LAMELLATION IN BRAIN UNRELATED TO SPONGIFORM ENCEPHALOPATHY

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SUMMARY

When sections from the cerebral cortex of 5 normal rats and 2 normal monkeys were stained with saturated aqueous uranyl acetate (without block staining) and examined with the electron microscope, all 7 animal brains showed abundant membrane lamellation between apposed neuronal and neuroglial processes. Such lamellations match those described by Beck *et al.* (1982) in the brains of kuru-inoculated monkeys in their early stages before spongiform encephalopathy has become established. The present observations question their contention that membrane lamellation is a real phenomenon and a prelude to spongiform change in kuru encephalopathy in the monkey.

INTRODUCTION

The ultrastructure of spongy vacuoles in spongiform encephalopathy (scrapie, kuru and Creutzfeldt-Jacob disease) is now well documented. For example, Kidd (1967) and Landis *et al.* (1981) showed that the vacuoles occur in neurons (dendrites, axons and axon terminals and neuronal perikarya). The evidence for vacuolation in neuroglia is less convincing (Kim and Manuelidis, 1983). The vacuoles may be up to 50 to 100 μm in diameter (Adam *et al.*, 1982) and appear in EM sections as gross swellings of focal regions of the neuronal processes with apparent fragmentation of the surface membranes and loss of the internal organelles (cytomembranes, mitochondria, microtubules and neurofilaments). The only detailed studies of the early changes in spongiform encephalopathy are by Beck *et al.* (1975, 1982). These authors described, in the brains of monkeys inoculated two to three months before with kuru material, membrane lamellation which could no longer be detected at the onset of the spongiform lesions. Beck *et al.* (1975, 1982) stained their sections with uranyl acetate and lead citrate on the grid, but gave no further details of their methods. The present study was therefore undertaken to observe the effects of various staining methods, in particular the use of saturated aqueous uranyl acetate in various combinations. All the material described in this paper is from entirely 'normal' brains and it will be shown that when sections are stained with saturated aqueous uranyl acetate, membrane lamellation becomes evident, the lamellae being an apparent facsimile of those decribed by Beck *et al.* (1982).

MATERIAL AND METHODS

A. Five rats and 2 monkeys were used in this group. Five adult Wistar rats aged between 2 and 3 months were obtained from the animal house from different batches over several months. Three were perfused with 3 per cent cacodylate-buffered glutaraldehyde and the brains (occipital cortex) were diced into 1 mm cubes and postfixed in 1 per cent buffered osmium tetroxide. The brains of the other 2 animals were immersion-fixed in 3 per cent glutaraldehyde and then treated as for the previous 3 animals. The pieces were dehydrated in ethanol *without* block staining and embedded in Araldite. Sections were stained in saturated aqueous uranyl acetate (pH 5.5, 36° C.) for 10 min to 1 hr. Other sections were stained at room temperature. Residual uranyl acetate was retained at the bottom of the staining solution to indicate complete saturation. The sections on the grid are not easily wetted in this solution and it is essential to push the grids forcibly through the surface film and hold them under for 1 min or so before they sink and come to rest on the undissolved uranyl acetate. Simply floating the grids (sections downwards) does not ensure wetting of the sections for they may remain outside the surface film and spurious absence of staining may result. The sixth animal was a neonate marmoset monkey. For this animal, 1 mm cubes of cingulate cortex were fixed in 4 per cent cacodylate-buffered glutaraldehyde. Thereafter the procedure followed that employed for the rats. The seventh animal was an adult baboon, aged 4 years (occipital cortex), fixed and processed as for the neonate marmoset.

B. Pieces from 2 of the perfused rats (Method A) were block-stained in 1 per cent aqueous uranyl acetate, either at room temperature or 36° C for 20 min to 1 hr, dehydrated in ethanol and embedded in Araldite as above. Sections were stained with lead citrate.

C. Over the years well over a hundred aldehyde-perfused or immersion-fixed rat, guinea pig, monkey, fish, amphibian, reptile, bird and various invertebrate brains have been studied using aqueous uranyl block staining with lead on the section (as in Method B).

D. 1 mm cubes of rat occipital cortex or synaptosomes from other rats were fixed in 3 per cent cacodylate-buffered glutaraldehyde containing 4 per cent tannic acid to produce artefactual myelin forms (*see text and* Gray *et al.*, 1982*a*, *b*). Thereafter processing followed Method C.

Sections were viewed with a Philips EM 301 operating at 80 kV and equipped with a eucentric goniometer stage to give tilts through ± 40 deg. Careful alignment of the membrane lamellae in the electron beam ensured optimal definition. Objective lens astigmatism was corrected for each photographic exposure (although fig. 4A is slightly astigmatic). Numerous trials with the purposeful introduction of astigmatism and with through-focus series confirmed that the membrane lamellations described below were not the result of astigmatism, nor were they out-of-focus effects. Both can, of course, cause spurious images. Technical problems are considered further in the Discussion.

RESULTS

Figs. 1A, 2A and 2B illustrate lamellated membrane plaques as seen in the cerebral cortex of 5 normal rats with no block staining and with uranyl acetate followed by lead citrate, both on the section (Method A). The plaques showed up to 12 lamellae (*see below*), occurring between both neuronal and astrocytic juxtaposed membranes. In sections, the lengths of the plaques varied from about 0.1 μm to 1 μm with a peak at about 0.4 μm. In the cerebral cortex the frequency of occurrence varied widely. Areas of sections with large neurons or blood vessels showed few lamellated plaques because of the dearth of apposed membranes. An average figure is about 30 lamellate plaques per 100 μm^2 of section. Fig. 1 illustrates an exceptionally dense distribution with 10 plaques (arrow heads) in 12 μm^2 of section. The low magnification of fig. 1 does not permit visualization of the lamellation within the

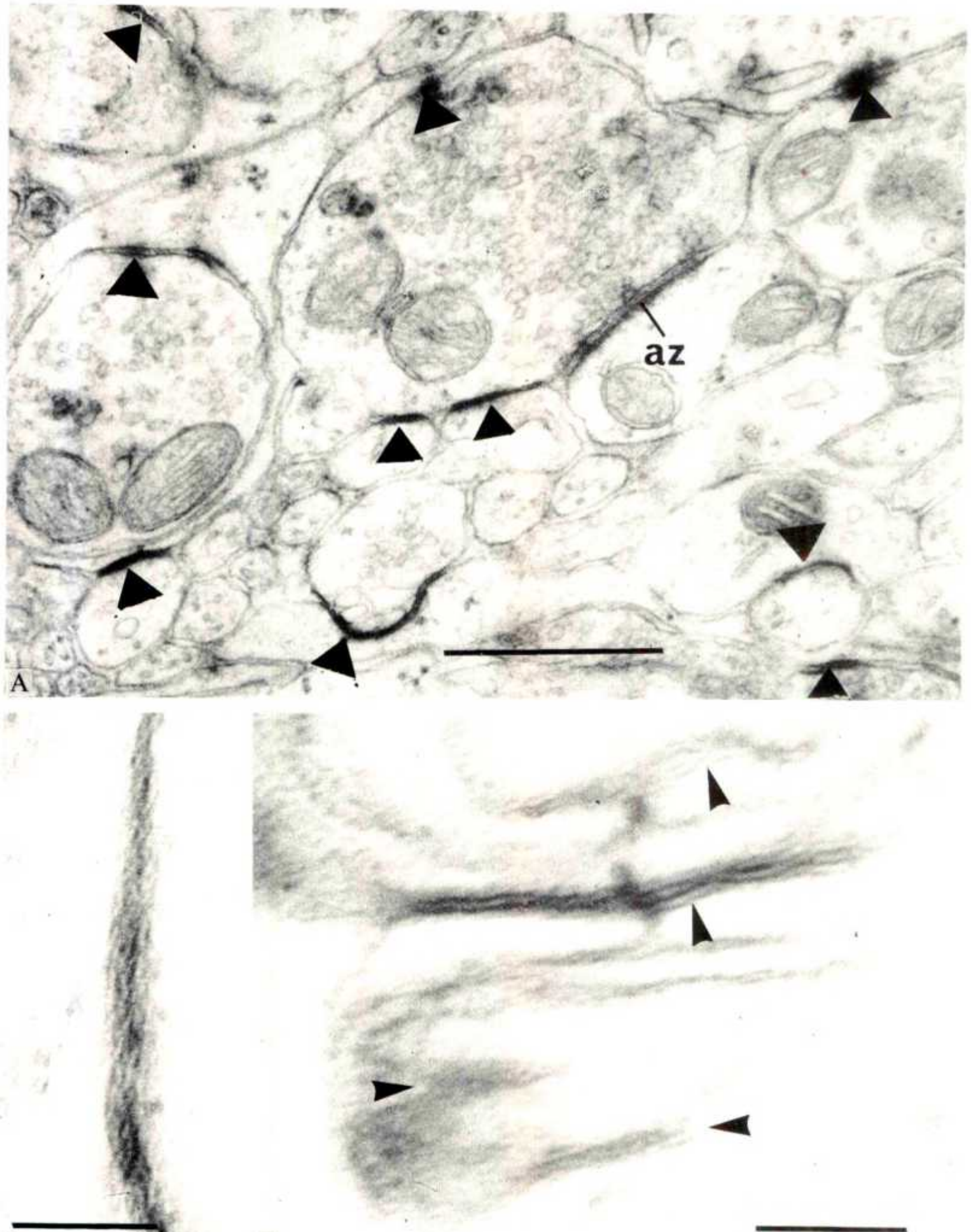

FIG. 1. A, low magnification electron micrograph of adult rat cerebral cortex showing a region with a high density of membrane lamellations (*arrow heads*); az = active zone. B and C, lamellated membranes (*arrow heads*) in cerebral cortex of adult baboon (both Method A). Calibration bar, A = 1 μm; B, C = 0.1 μm.

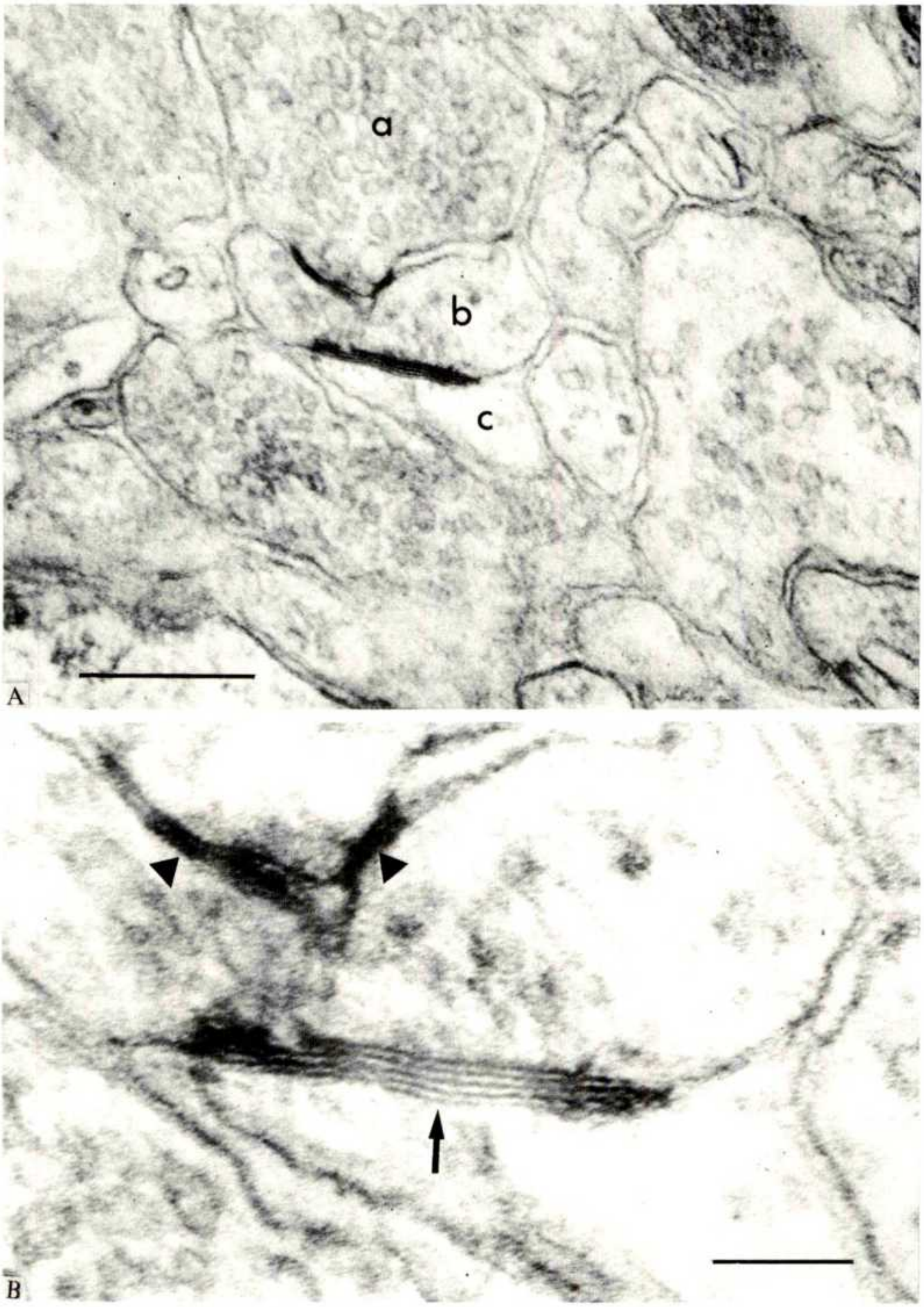

FIG. 2. A, medium magnification of adult rat cerebral cortex enlarged in B (Method A); a = axon terminal, b = dendrite, c = probable unmyelinated axon. Calibration bar, A = 0.5 μm; B = 0.1 μm.

plaque. To observe the lamellation on the EM screen a magnification of × 40 000 or more is needed.

Figs. 2A and B (cortex of normal rat) show the plaques at higher magnification. In fig. 2A they are seen in the neuropil, occurring between an axon terminal (a), dendrite (b) and probably an unmyelinated axon (c). Fig. 2B, at higher magnification, shows the lower plaque (of fig. 2A) to have five lamellae (arrow); the upper 2 plaques (arrow heads) run obliquely in the section and their lamellation is obscured (but revealed by tilting). The lower plaque (arrow) has a centre-to-centre spacing of the lamellae of about 6 to 7 nm, the dense lines being about 2 nm thick and the intervening zones 4 to 5 nm across. The plaques described below show the same measurements.

Some plaques (Method A) have up to 12 lamellae. In fig. 3A, where a dendrite (d), receiving a type 1 synapse at s, makes a lamellated plaque (p) with an unidentified profile (z), at least 10 lamellae can be distinguished (inset).

The active zones of the apposed synaptic membranes never showed lamellation, presumably reflecting the well-known stability of this region of the cleft (*see* Gray, 1959), as for the active zone (az) of the Type 1 synapse in fig. 1A. However, regions of the cleft close to the active zone (az, fig. 3B) sometimes show lamellation. Here (arrow) at least 9 lamellae are apparent at this type 2 synapse.

When a lamellate plaque is tilted in the electron beam with the eucentric goniometer, the lamellae only remain apparent through ± 5 deg. A plaque with six clear lamellae was chosen with zero tilt and tilted first through 10 deg (fig. 4A). At this point the lamellae begin to vanish and at 25 deg tilt (fig. 4B) appear in parts as a blur (a), but in other parts (b) polygonal subunits 7 to 8 nm across can be discerned. Since the electron beam is, as it were, 'looking through' six oblique lamellae, all lamellae will be superimposed in the path of the beam and presumably the mosaic will only appear when the subunits of each lamella are in register.

To determine which of the two section stains, lead citrate or uranyl acetate, is critical for the display of membrane lamellation, alternate sections from the same block face were stained either with saturated aqueous uranyl acetate alone (Method A, no block staining) or with lead citrate alone (Method A). Membrane lamellated plaques occurred equally commonly with double staining as when uranyl acetate was used alone (fig. 4C), although, as would be expected, the overall contrast was lower than with the combined lead staining. Adjacent sections from the same block face stained with lead only (and sections from other animals from the Method A group treated the same way) never showed lamellated membranes, nor did they show any expanded unstained zones within apposed membranes that could represent the basis for lamellated plaques. Fig. 5B shows such a section from the same block face and adjacent to sections showing lamellations with saturated uranyl acetate. No lamellated plaques can be seen. Very rarely dense membrane appositions (fig. 5B, b) can be seen. They are presumably focal points of poor fixation (certainly not gap or tight junctions), where the membranes have collapsed against each other and a faint unit membrane structure can be seen (fig. 5B, b, enlarged in the inset). Such points of membrane collapse can occasionally be seen in the best fixed

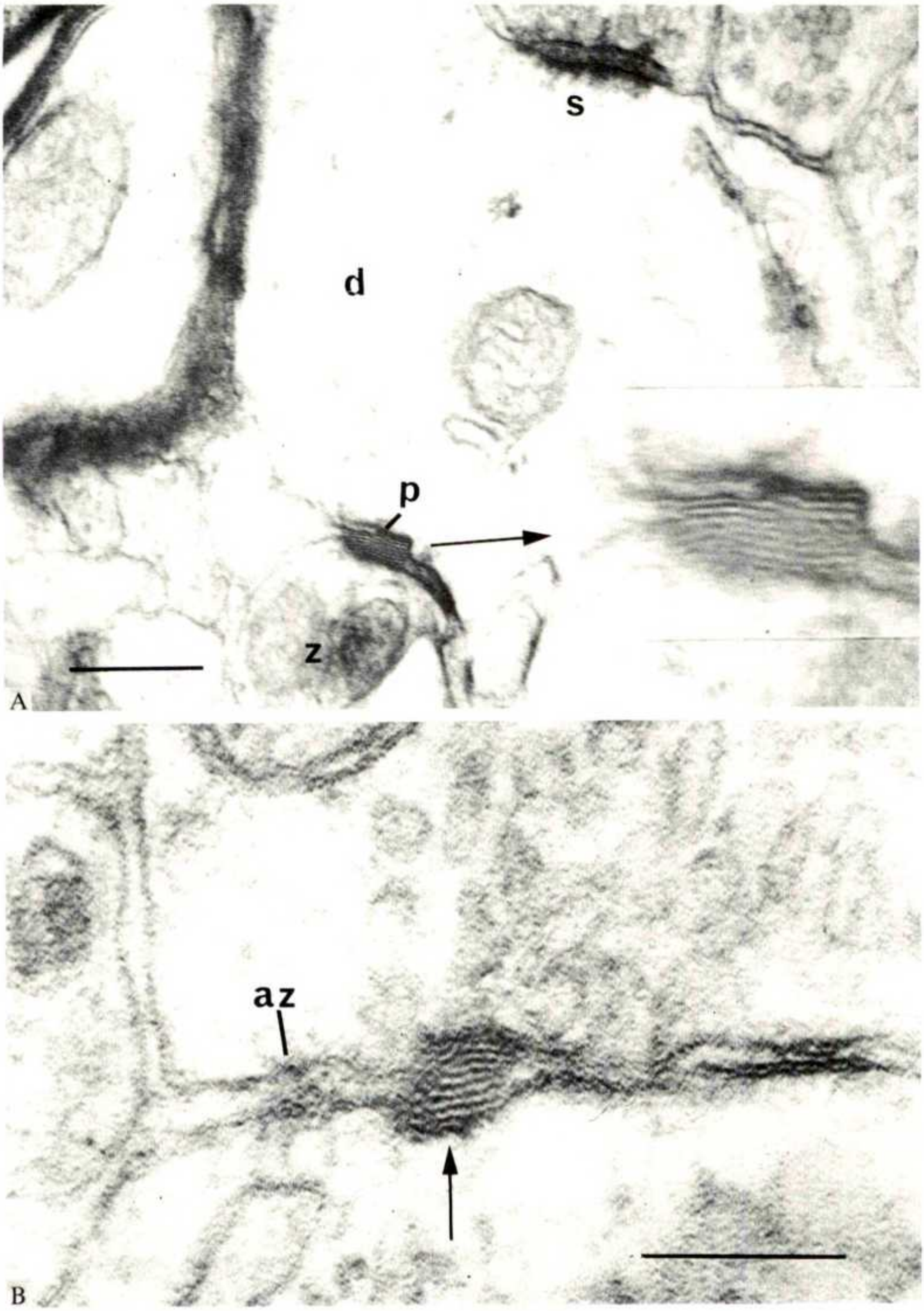

FIG. 3. A, dendrite (d) with a highly lamellated plaque (p) enlarged in inset; s = synapse, z = unidentified profile. B, membrane lamellation close to an active zone (az) in a type 2 synaptic cleft. (Both Method A, adult rat). Calibration bar, A = 0.5 μm, *inset* = 0.1 μm; B = 0.2 μm.

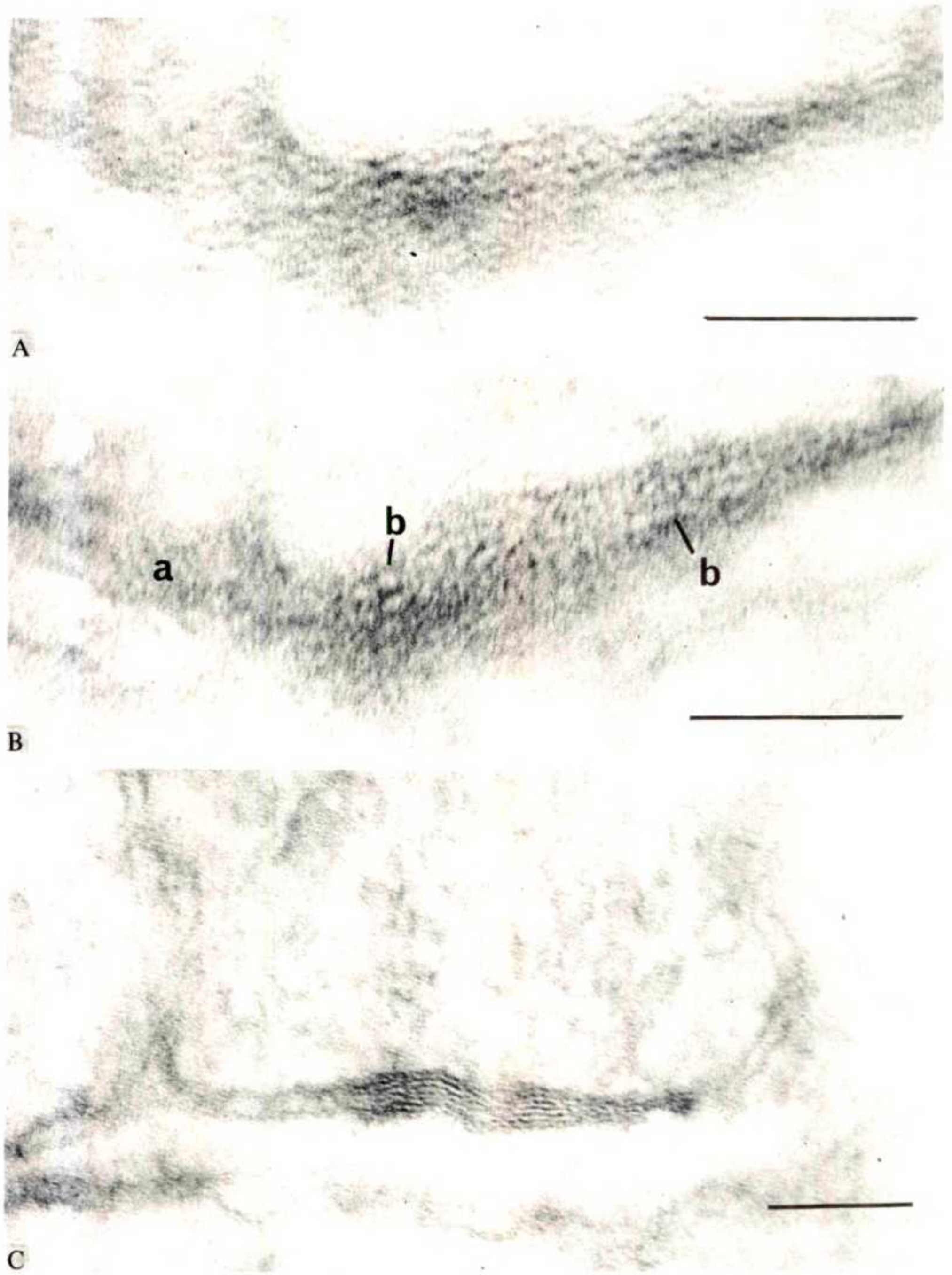

FIG. 4. A and B, 10 deg and 25 deg tilts, respectively, of a lamellated plaque (Method A); a = blurred region, b = polygonal subunits. C, lamellated plaque stained on the section with saturated aqueous uranyl acetate and without lead (Method A, adult rat). Calibration bar, A, B = 0.1 μm; C = 0.2 μm.

material and often appear in published micrographs (e.g. figs. 145 and 177 of Palay and Chan-Palay, 1974).

So far it has been shown that lamellated membranes are formed without block staining and that the only essential procedure is treatment with saturated aqueous uranyl acetate on the section. The uranyl radical is apparently precipitated in the plastic of the section in a periodic array. To determine the effect of block staining before dehydration, with the conventional 1 per cent aqueous uranyl acetate, some of the pieces treated by Method A were stained in this way (Method B). Subsequent staining of the sections with saturated aqueous uranyl acetate showed no membrane lamellation, with or without additional lead staining. No illustrations are required: taken in conjunction, Methods B and C have been used by us on innumerable animals and pictures have been published by many authors using these methods showing no membrane lamellation.

All the observations described so far have been from the 5 adult rats (cerebral cortex). To pursue the investigations further the cortex from primates was examined—normal adult baboon and neonatal marmoset (*see below*). With Method A (no block staining and saturated aqueous uranyl acetate on the section) the baboon cortex showed abundant membrane lamellations (fig. 1B and C). Neonatal monkey cortex was chosen for examination (Method A) since at this stage the immature axons, dendrites and neuroglia have only limited areas of contact and large extracellular gaps (fig. 5A, g), up to 1μm across, not present in the mature cortex, are common. Nevertheless lamellated plaques (arrows) were common when two processes were in close apposition (fig. 5A, inset). No plaques were found along single unapposed membranes.

Next it was of interest to determine whether lamellated plaques occur between apposed neuroglial processes in the adult cortex. Even in the best perfusion or immersion-fixed brain, perivascular astrocytes often show membrane fragmentation and generally bad fixation. Such appearances are usually excluded from published micrographs. They were occasionally encountered in conventional preparations of the present work (Methods B and C), where the membranes appeared broken into short lengths and twisted or otherwise fragmented. However, when Method A was applied (no block staining and saturated aqueous uranyl acetate on the section), the fragmented membranes showed prominent lamellation. Fig. 6A shows three adjacent perivascular astrocyte end-feet (a) on a capillary (lumen l). The insets show the membrane fragments at high magnification. The lamellation is indisputable. Fig. 6B is taken from another badly fixed perivascular astrocyte stained with saturated aqueous uranyl acetate (Method A) and again illustrates the bizarre lamellation produced by this method, in these last two cases on badly fixed fragmented membranes.

Finally, to investigate whether the above membrane lamellations are related to myelin figures, such figures were produced in fragments and synaptosomes of rat brain cortex by adding tannic acid to the initial aldehyde fixative (Method D). These were seen in experiments described in Gray *et al.* (1982*a*, *b*). Myelin figures are

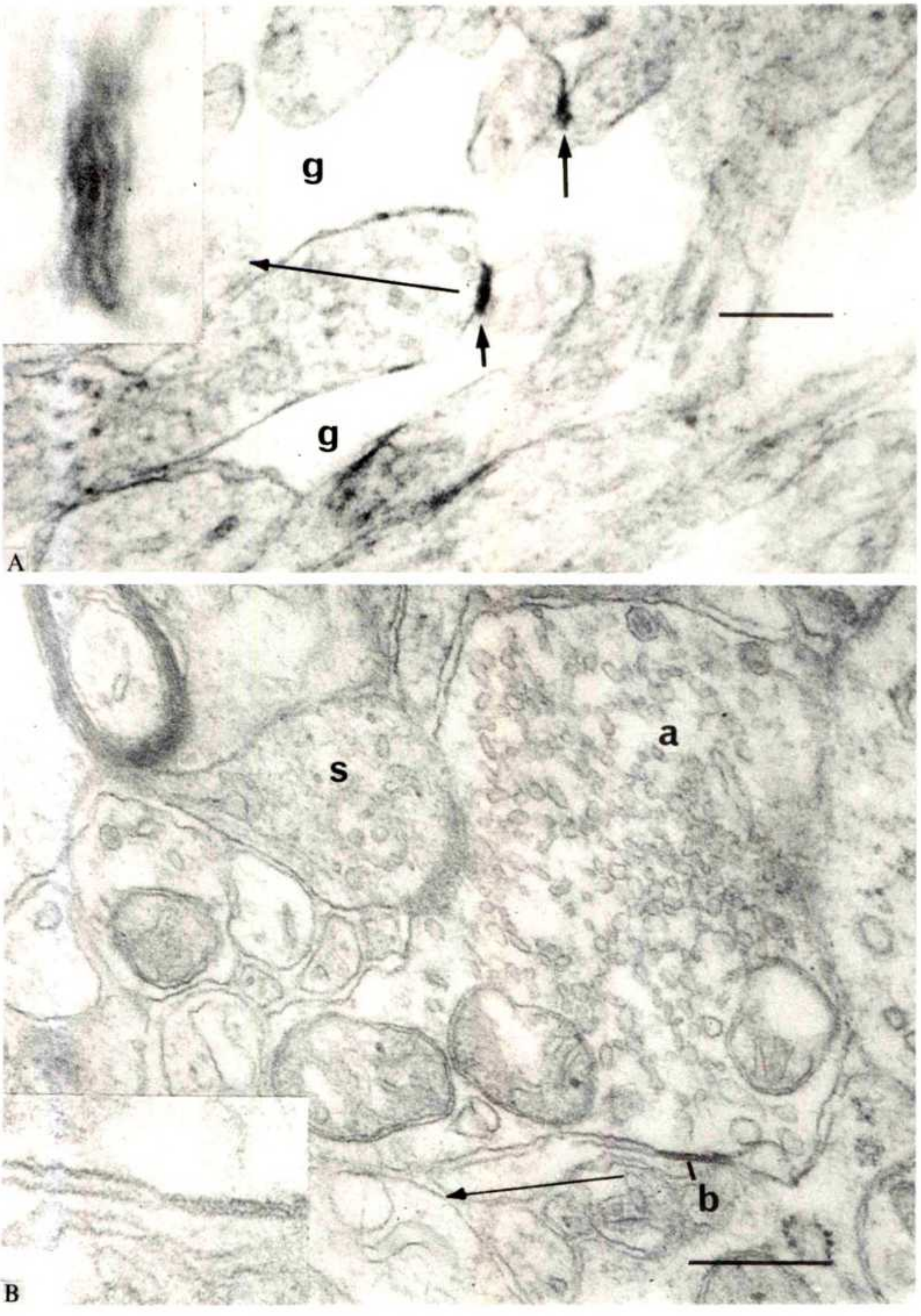

FIG. 5. A, neonatal monkey showing the typical preadult large extracellular spaces (g) and lamellated plaques where the processes come into apposition (Method A). B, adult rat brain, showing axon terminal (a) synapsing with dendritic spine (s); section stained with lead citrate but no uranyl acetate. Lamellated plaques are never seen under these conditions, only rare points of membrane collapse (b) presumably due to bad fixation (Method A). Calibration bar, A = 0.3 μm, *inset* = 42 nm; B = 0.5 μm, *inset* = 70 nm.

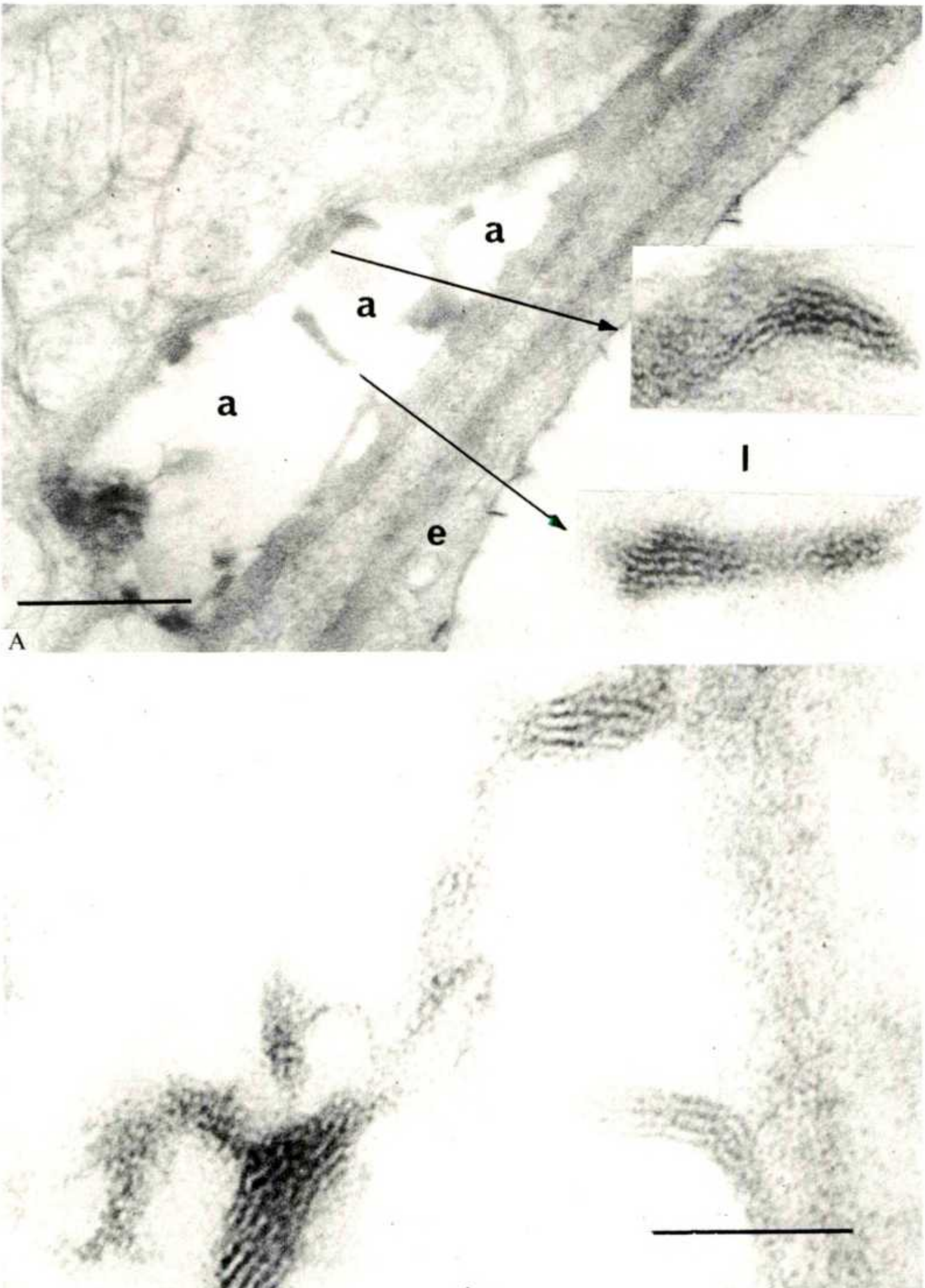

FIG. 6. A, adult rat brain. Poorly fixed pericapillary astrocytic end-feet (a) with fragmented membrane, which show lamellation at high magnification (*insets*), e = capillary endothelium, l = lumen. B, some bizarre lamellated fragments are shown from another pericapillary astrocyte (Method A). Calibration bar, A = 0.4 μm, *insets* = 90 nm; B = 0.1 μm.

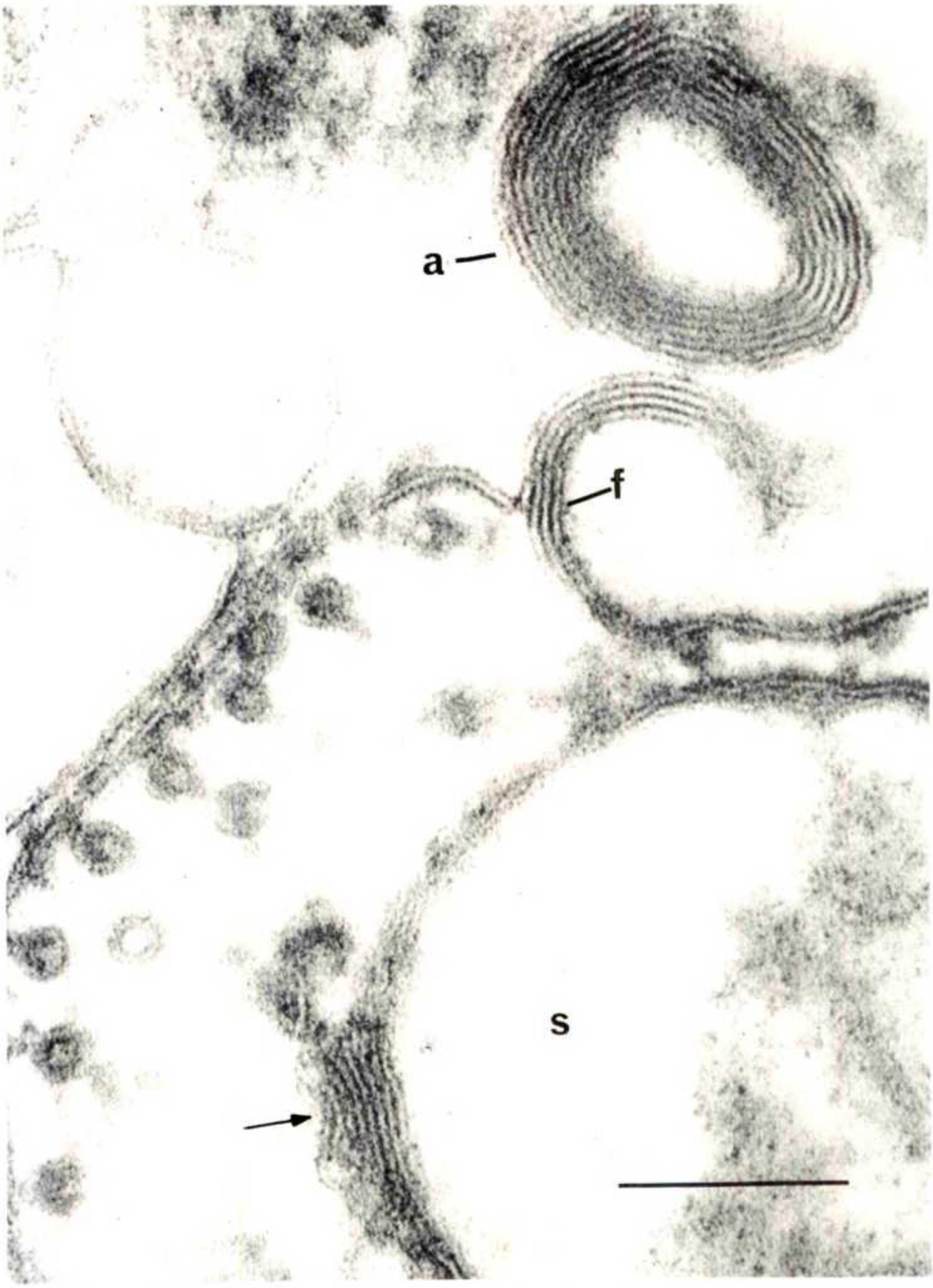

FIG. 7. Adult rat. Tannic acid has been added to the aldehyde fixative to produce myelin forms. They differ from the lamellated plaques, which never appear as outgrowths of ruptured membranes (Method D); a and f = myelin figures, s = swollen mitochondrion. Calibration bar = 0.1 μm.

artefacts that are produced when the unsaturated lipids of membrane fragments are brought into contact with an aqueous phase. They can be seen growing out 'worm-like' from the fragments with the light microscope and can be fixed and studied in sections with the electron microscope (Engström and Finean, 1958). Fig. 7 shows a synaptosome with a myelin form (f) developed at the point of rupture of the membrane. Another (arrow) has formed on the border of a grossly swollen mitochondrion (s). A third (a) is tubular and is seen in cross section. Typical of myelin figures, they show no alternation of dense and pale (intraperiod) lines in contrast to true myelin. In this respect they resemble the lamellated membranes that are the subject of this paper and they have a similar 7 nm periodicity. Unlike the myelin forms, however, the lamellated membranes are clearly not outgrowths at fractured membrane foci and seem only to occur at the site of two juxtaposed membranes.

DISCUSSION

The ultrastructure of the pathogenic agent which leads eventually to spongiform encephalopathy remains obscure and is beyond the scope of this paper. Here the problem of the detection of the initial changes which may arise before spongiform vacuolation becomes apparent is examined. Such changes are, of course, more likely to be detected by electron microscopy than by light microscopy. In the past the only evidence for early changes is that of Beck *et al.* (1975, 1982), who described membrane lamellation occurring in monkey brains (first passage kuru) with a peak at three to four months and thereafter disappearing before the onset of the spongy vacuoles (*see* Introduction). These authors provided only scanty evidence as to how one relates to the other, yet nevertheless speculated that membrane lamellation is a prelude to and somehow initiates the formation of the spongy vacuoles. They found no lamellation in 3 control monkeys.

Detailed studies were therefore made in the present work of the staining effects on the cerebral cortex of 5 normal rats and 2 normal monkeys (*see* Methods), particularly the effect of staining the sections for electron microscopy for up to 1 h with saturated aqueous uranyl acetate, since Beck *et al.* (1975, 1982) gave no details of their staining methods. In the present work in sections of the cerebral cortex of all 7 animals, stained with saturated aqueous uranyl acetate, extensive membrane lamellation was found, apparently the facsimile of that described in kuru-inoculated monkey brain by Beck *et al.* (1975, 1982).

Since Beck *et al.* gave no details of their staining methods, they no doubt assumed that stains only contrast in different ways and were obviously not aware that saturated aqueous uranyl acetate could produce spurious lamellation at membrane apposition sites in the plastic section. This was a reasonable assumption, just as, in the present work, the lamellations produced with uranyl acetate came as a complete surprise. Such lamellation, in normal brain tissue, has apparently never been reported by other workers. This is no doubt, first, because the use of saturated aqueous uranyl acetate is unconventional—most workers use a 1 or 2 per cent aqueous solution, either on the block during dehydration or on the sections on the grid or both. Secondly, the lamellation of the plaques is not apparent at the lower (and most used) magnifications of the electron microscope—it only becomes apparent at about × 40 000. At this relatively high magnification, the intensity of the image on the EM screen falls markedly and the operator is literally working in the dark.

Why does saturated aqueous uranyl acetate produce lamellation with a 6 to 7 nm periodicity in plastic sections of pairs of apposed membranes (neuronal and glial) in brain? This is a problem best referred to the biophysicist. Possibly focal points of poor fixation or sinks of Ca^{++} ions in the extracellular clefts somehow cause intense binding of the uranyl radical so that at these points saturation is lost and waves of saturated and unsaturated faces propagate outwards through the plastic and the paired membrane structure is obliterated. It is well known, of course, that uranyl and lead cations penetrate readily through the plastic section although they are in an aqueous phase (personal observations on stereo-pairs of micrographs). Thus uranyl cations can just as readily move *laterally* within the Araldite plastic.

ACKNOWLEDGEMENTS

I am grateful to Dr L. E. Westrum, Professor of Neurosurgery, University of Washington, for perfusing one of the rats and giving an independent assessment of my data, and also to The Wellcome Trust for financial support.

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Brain (1985), **108,** 153–154

A NOTE ON MEMBRANE LAMELLATION

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Gray (1985) considers the appearances of membrane lamellation in the brains of kuru-inoculated spider monkeys during early incubation (Beck *et al.*, 1982) to be artefactual. He bases his opinion on the fact that he has seen similar multilamellated membranes in the cerebral cortex of normal rats and monkeys when material was not block-stained with 1 per cent aqueous uranyl acetate before dehydration and when subsequent sections were stained either with aqueous uranyl acetate, pH 5.5, saturated at 36° C (Method A) or were double-stained with uranyl acetate and lead citrate. Staining with lead citrate alone did not produce membrane lamellation. He found that in neighbouring blocks from the same animals which were treated with 1 per cent aqueous uranyl acetate, the sections being either double-stained with uranium and lead, or with either of these alone, lamellated membranes were not seen (Method B).

In the technique which we employed and which was given in our earlier paper (Beck *et al.* 1975, p. 597, referred to in Beck *et al.*, 1982, p. 756), the same material being used in both papers, the kuru-inoculated and control monkeys were both perfused with a 1 per cent phosphate-buffered glutaraldehyde/paraformaldehyde mixture. The blocks were postfixed in 1 per cent buffered osmium tetroxide followed by 2 per cent maleic acid-buffered uranyl acetate, dehydrated and embedded in Araldite. Sections were stained with aqueous uranyl acetate, pH 4.0, saturated at 10° C (approximately 4–5 %) and lead citrate. Unfortunately the block treatment with uranyl acetate was not mentioned in our description, so that Gray (1985) assumed that our material had not been block-treated. Of the 9 inoculated monkeys reported in our paper, 7, from 4 to 40 weeks after inoculation, showed lamellated membranes which we termed abnormal configurations of plasma membranes (ACPMs). Two did not show such lamellated membranes, one at 2 weeks after inoculation, the other at 122 weeks when the disease was fully developed. Three controls did not show membrane lamellation. All the spider monkeys were adolescents or young adults. If ACPMs were an artefact, then according to Gray's criteria, none of our cases should have shown lamellated membranes, since they were all block-treated with uranyl acetate.

We have since recut some of this monkey material and applied the same staining methods to the sections as in our 1982 paper. The results were identical, ACPMs being observed in the inoculated monkeys and none in 3 normal controls. The grids have also been examined by an independent observer. Variations in the staining of sections from kuru-inoculated animals gave the following results. (1) Double-staining with saturated alcoholic uranyl acetate (in equal volumes of 50 % ethanol and 100 % methanol) and lead citrate showed ACPMs; (2) staining with lead citrate or (3) saturated aqueous uranyl acetate, pH 4.0, alone, showed ACPMs at somewhat reduced contrast, especially with the latter stain.

We were naturally disturbed by Gray's findings and searched for an explanation other than 'artefact'. Since all our animals were young, it occurred to us that membrane lamellation might be a feature of the normal aged brain. We therefore examined the brains of 2 aged BD IX rats (16 months old) which were perfused with a 2 per cent cacodylate-buffered formaldehyde/glutaraldehyde mixture. From each brain we took two neighbouring blocks of dorsal and occipital cortex. One block from each region was treated like those of the spider monkeys, except that saturated alcoholic uranyl acetate (approximately 10 %) was used for contrasting instead of 2 per cent maleic acid-buffered; in its neighbour block-treatment with uranyl acetate was omitted, to match the technical variation (Method A) applied by Gray. Sections from both blocks were double-stained according to the technique used for the monkey material. One of the old rats showed a few ACPMs in both of the neighbouring blocks, the other showed no membrane lamellation in either. Additional sections of the latter, from the same block face, were stained with saturated aqueous uranyl acetate pH 5.5 (Gray's Method A), either alone or double-stained with lead citrate. These sections were also negative. If Gray is right in suggesting that this method causes artefactual membrane lamellation, it is surprising that we did not find any lamellae in this normal rat.

We are at a loss to explain the discrepancy between Gray's and our own findings. It is noted, however, that (1) we found ACPMs in two different groups of animals in material treated with different techniques, both of which differed in only minor details from Gray's Method B; (2) that according to Gray, in blocks stained with uranyl acetate (at least with a 1 % aqueous solution) lamellated membranes are not found; (3) that none of our controls showed ACPMs; and (4) that ACPMs were observed in sections stained with lead citrate alone. In view of these observations we do not regard ACPMs in kuru-inoculated monkeys and in one aged rat as artefacts due to fortuitous technical treatment, but believe that they are formed during life.

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(*Received May 29, 1984. Revised August 21, 1984. Accepted August 30, 1984*)

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EFFECTS OF AGEING ON LOCAL RATES OF CEREBRAL PROTEIN SYNTHESIS IN SPRAGUE-DAWLEY RATS

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SUMMARY

The effects of ageing on local rates of protein synthesis in 39 brain structures in resting conscious rats have been examined. Young adult rats (aged 6 months) have been compared with a group of middle-aged/aged rats (aged 15–23 months). The results show that ageing is associated with significant decreases in rates of protein synthesis in the brain as a whole as well as in several specific brain regions. Brain regions involved in visual and auditory function were selectively affected, perhaps due to a chronic lack of sensory input. Several regions involved in motor function and two areas in the limbic system had significantly decreased rates of protein synthesis in the old rats. Notably, there was a significant age-related decrease in protein synthesis in the locus coeruleus which contains the cell bodies of origin of the major ascending noradrenergic innervation of the cortex.

INTRODUCTION

Senescent changes in brain structure and function are well known, but the underlying causes of these changes are poorly understood. In man, psychological testing has shown impairments in cognitive functions (Birren *et al.*, 1963; Granick and Patterson, 1971). These changes are accompanied by a reduction in average glucose consumption of the brain as a whole even while cerebral blood flow and oxygen consumption may remain within the normal range (Dastur *et al.*, 1963). In addition, degenerative changes such as neuronal loss and dendritic regression can be found postmortem in some brain regions in normal aged subjects (Brody, 1955; Scheibel *et al.*, 1975). In rats, ageing is also accompanied by behavioural as well as histopathological changes in the brain (Feldman, 1976; Vaughan, 1977; Ordy *et al.*, 1978). Studies with the deoxyglucose method have demonstrated that age-related, region-selective reductions in glucose utilization occur in both Sprague-Dawley (Smith *et al.*, 1980*b*) and Fisher-344 rats (London *et al.*, 1981). Most brain regions that are associated with visual and auditory functions show significant reductions in glucose utilization that may be secondary to degenerative changes in the primary sense organs. With only a few exceptions the rates of glucose utilization in the structures of the limbic and motor systems of the rat remain unchanged with age.

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Measurements of energy metabolism do not differentiate between the immediate functional demands of cerebral structures and the longer term maintenance processes within the nervous system. Long-term effects that are related to changes in morphology, structural maintenance, and remodelling in the nervous system are more likely to be reflected in biosynthetic biochemical processes, such as protein synthesis. In this study the effects of ageing on local rates of protein synthesis in brain have been examined by means of a quantitative autoradiographic method (Smith *et al.*, 1980*a*). The results of these studies show that in middle-aged and aged rats, as compared with young adult animals, the overall rate of cerebral protein synthesis is decreased. On a local level some specific structures are affected, notably the locus coeruleus, substantia nigra, and structures associated with visual and auditory functions.

MATERIALS AND METHODS

Animals

Normal male Sprague-Dawley albino rats between the ages of 6 and 23 months were obtained from Zivic Miller Laboratories, PA. Studies were completed in 6 young adult rats (6 months of age), 8 middle-aged rats (15 months of age), and 4 aged rats (22–23 months of age). The animals were group-housed (2–3 per cage) under a laminar flow hood designed to reduce the exposure to infectious agents. The animals were maintained on Purina Laboratory Chow and water *ad libitum* until 14 h prior to the measurement of protein synthesis at which time they were deprived of food. The physiological state of the animals at the time of the measurements of protein synthesis was assessed by monitoring rectal temperature, mean arterial blood pressure, haematocrit, and arterial blood pH, pCO_2 and pO_2. Only animals with values for these physiological variables within the normal range (Sokoloff *et al.*, 1977) were included in these studies.

Determination of Local Rates of Protein Synthesis

Local rates of protein synthesis were determined by means of a recently developed autoradiographic method (Smith *et al.*, 1980*a*). A more detailed description of this method has been published elsewhere (Smith *et al.*, 1984). The method is based on the use of L-[1-^{14}C]leucine as a tracer to measure leucine incorporation into protein. Carboxyl-labelled leucine has been chosen as the tracer because the only pathway for its metabolic degradation entails a transamination followed by decarboxylation. Therefore, in the metabolism of L-[1-^{14}C]leucine the label is transiently transferred to α-ketoisocaproic acid and ultimately to $^{14}CO_2$ which is negligibly reincorporated because of dilution by the large amount of unlabelled CO_2 produced by cerebral carbohydrate metabolism (Banker and Cotman, 1971). There are, therefore, no residual radioactive products of [^{14}C]carboxyl-labelled leucine other than the labelled protein. By mathematical analysis of the kinetics of exchange of leucine between plasma and tissue, its metabolic degradation and its incorporation into protein, an equation (fig. 1) has been derived that defines the rate of L-leucine incorporation into protein in terms of the time course of the plasma L-leucine specific activity, the final tissue concentration of ^{14}C, and experimentally determined rate constants.

$$v_i = \frac{C_i^*(T) - C_e^*(T)}{\int_0^T \left(\frac{C_p^*}{C_p}\right) dt - e^{-(k_2+k_3+k_4)T} \int_0^T \left(\frac{C_p^*}{C_p}\right) e^{(k_2+k_3+k_4)t} dt}$$

FIG. 1. Operational equation for calculation of local rates of protein synthesis (v_i). C_p and C_p^* represent the concentrations of free leucine and [1-^{14}C]leucine, respectively, in the arterial plasma. $C_i^*(T)$ represents the total tissue concentration of ^{14}C determined by the quantitative autoradiographic technique. The constants k_1, k_2, k_3 and k_4, represent the rate constants for carrier-mediated transport of leucine from plasma to tissue, for carrier-mediated transport back from tissue to plasma, for metabolic degradation of leucine, and for incorporation of leucine into protein, respectively. The numerator of the equation is the total amount of label incorporated into protein in the tissue at the end of the experiment. It is calculated from the total amount of label in the tissue, $C_i^*(T)$, minus the free [^{14}C]leucine in the tissue, $C_e^*(T)$. $C_e^*(T)$ is estimated as follows:

$$k_1 e^{-(k_2+k_3+k_4)T} \int_0^T C_p^* e^{(k_2+k_3+k_4)t}\, dt.$$

In a separate series of animals, $C_e^*(T)$ has been measured and determined to constitute less than 5 per cent of $C_i^*(T)$ 60 min after an i.v. pulse injection of [1-^{14}C]leucine. $C_e^*(T)$ can be reduced to zero by washing tissue sections repeatedly in 10 per cent phosphate buffered (pH 7) formalin. At the time of these ageing experiments, fixation in formalin vapour followed by washing in tap water was carried out rather than the immersion fixation and washing procedure. It was later found that the vapour fixation and washing procedure used in these experiments washed out only half of the unincorporated label. $C_e^*(T)$ in this study was therefore divided by 2. This was considered reasonable in view of the very small effect the second term in the numerator has on the final result and the fact that the study had been carried out on valuable, aged animals. In subsequent studies the procedure of immersion fixation followed by washing will be used routinely.

The animals were prepared for the determination of local rates of protein synthesis by the insertion under light halothane anaesthesia of polyethylene catheters into one femoral vein and artery. The rat's hindquarters were then restrained by the application of a loose-fitting plaster cast which was taped to a lead brick. After a period of 4 h for recovery from the effects of surgery and anaesthesia, the procedure was initiated by the administration of an intravenous pulse of L-[1-^{14}C]leucine (specific activity 59 mCi/mmol, Amersham Corporation, Arlington Heights, IL); the dose was 100 μCi/kg body weight contained in 0.1 to 0.4 ml of physiological saline. Timed arterial blood samples were then collected during the following 60 min for the determination of plasma concentrations of leucine and [^{14}C]leucine. The blood was immediately centrifuged to remove the red cells, and the plasma was stored on ice and assayed later. At the end of the 60 min experimental period the rats were killed by an intravenous injection of sodium pentobarbital, and the brains were quickly removed and frozen in isopentane cooled to -40°C with dry ice.

The brains were cut into sections 20 μm in thickness in a cryostat maintained at -18°C, and the sections were mounted on gelatin-coated glass slides and air dried. They were then fixed in 37 per cent formalin vapour overnight, and washed in running water for 1 h. This fixation and washing procedure was designed to remove unincorporated [^{14}C]leucine and any ^{14}C-labelled α-ketoisocaproic acid from the tissue sections without loss of labelled protein. The sections were then dried and autoradiographed along with calibrated [^{14}C]methylmethacrylate standards as previously described (Sokoloff *et al.*, 1977). Integrated optical densities of regions of the autoradiographs corresponding to selected brain structures were measured with either a manual densitometer (Photovolt Model 520-A densitometer, Photovolt Corporation, NY) equipped with a 0.2 mm aperture or with a Photoscan System P-1000 densitometer (Optronics International, Chelmsford, MA) as previously described (Goochee *et al.*, 1980). The structures on the autoradiographs were localized and identified by comparison with the

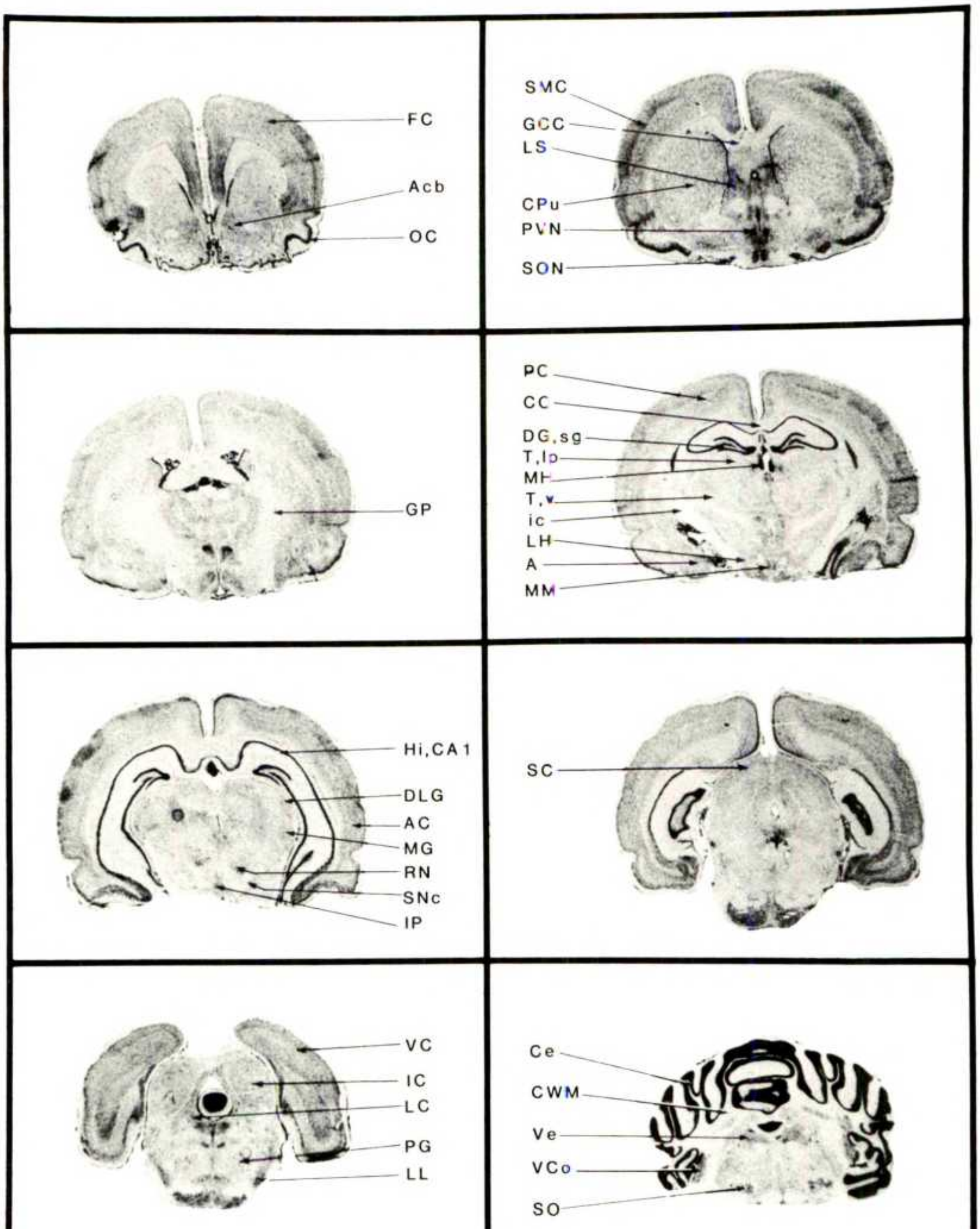

FIG. 2. Cresyl violet-stained sections of rat brain illustrating the location of the structures (Tables 3–5) in which rates of protein synthesis were determined. FC = frontal cortex; Acb = nucleus accumbens; OC = olfactory cortex; SMC = sensorimotor cortex; GCC = genu of the corpus callosum; LS = lateral septal nucleus; CPu = caudate putamen; PVN = paraventricular nucleus; SON = supraoptic nucleus; GP = globus pallidus; PC = parietal cortex; CC = corpus callosum; DG, sg = dentate gyrus, supragranular zone; T,lp = thalamus, lateral posterior; MH = medial habenula; T,v = ventral thalamus; ic = internal capsule; LH = lateral hypothalamus; A = amygdala; MM = mamillary body; Hi, CA1 = CA1 of hippocampus; DLG = dorsal lateral geniculate; AC = auditory cortex; MG = medial geniculate; RN = red nucleus; SNc = substantia nigra compacta; IP = interpenduncular nucleus; SC = superior colliculus; VC = visual cortex; IC = inferior colliculus; LC = locus coeruleus; PG = pontine grey; LL = lateral lemniscus; Ce = cerebellar cortex; CWM = cerebellar white matter; Ve = vestibular nucleus; VCo = ventral cochlear nucleus; SO = superior olivary nucleus.

atlas of König and Klippel (1963) and the cortical maps of Krieg (1946) (fig. 2). These optical densities were used to determine the local tissue concentrations of ^{14}C by comparison with the optical densities produced by the calibrated standards.

The plasma samples were deproteinized with 4 per cent sulphosalicylic acid, and [^{14}C]leucine and leucine concentrations were assayed by liquid scintillation counting and by amino acid analysis (Beckman Amino Acid Analyzer, Model 121 MB, Beckman Instruments, Fullerton, CA), respectively. It is necessary to deproteinize the plasma samples because a significant amount of [^{14}C]leucine is incorporated into plasma protein. From the time courses of the concentrations of [^{14}C]leucine and leucine in the deproteinized plasma and the local tissue concentration of ^{14}C, local rates of protein synthesis were calculated by means of the operational equation (fig. 1).

All calculations were carried out with a Hewlett-Packard System 9845B computer (Hewlett Packard, Loveland, CO).

RESULTS

Survival

The middle-aged and aged groups of rats used in the studies were derived from a population of retired breeders segregated specifically for ageing research at the age of 10 months. At the ages of 6, 15, and 22 to 23 months the survival rates of the populations were about 100, 91, and 26 per cent, respectively (Bruce Rose, Manager, Aged Rat Colony, Zivic Miller Laboratories, personal communication). Of the 31 rats obtained from Zivic Miller, 8 were young adults, 9 were middle-aged, and 14 were aged. None of the rats had any evidence of cataracts. One of the young animals was hypothermic, and one of the aged animals was hypotensive during the experiment. One each of the young adult and the middle-aged groups had brain tumours. In the aged group there was one case of each of the following: bowel tumour, lung tumour with metastases, lung tumour without metastases, pituitary tumour, fibroma of the abdominal wall, and an invasive tumour of the right hip. In addition, 3 of the aged rats died from bronchopneumonia, and 1 of these 3 animals had a pituitary tumour. All these animals were excluded from the study. This reduced the aged group to 4 and the percentage of 'survivors' in this group to 7 per cent. In the middle-aged group the number was reduced to 8 which represented 81 per cent of the original population. Because the aged group was too small for statistical evaluation, the aged and middle-aged animals were combined to form a group of old rats with an age span of 15 to 23 months. These survivors represent about 60 per cent of the original population. There were no statistically significant differences in rates of protein synthesis in any brain structures between the 4 aged and 8 middle-aged animals, and the values found in the two groups overlapped completely.

Physiological Status

There were no significant differences in the physiological status of the 2 groups of animals (Table 1). Only body weight exhibited an age-related change; body weight was higher in the older group of animals as compared with the young adults.

TABLE 1. PHYSIOLOGICAL VARIABLES IN YOUNG AND OLD RATS DURING MEASUREMENT OF LOCAL RATES OF CEREBRAL PROTEIN SYNTHESIS†

Parameter	*Young adult* *(6)*	*Middle-aged/aged* *(12)*
Body weight (g)	771 ± 30	879 ± 21*
Haematocrit (%)	50 ± 3	46 ± 1
Mean arterial blood pressure (mmHg)	117 ± 3	118 ± 2
Arterial blood pH	7.46 ± 0.01	7.44 ± 0.01
Arterial blood pO_2 (mmHg)	82.4 ± 2.1	81.6 ± 1.1
Arterial blood pCO_2 (mmHg)	35.3 ± 1.0	34.6 ± 0.4
Arterial plasma leucine concentration (nmol/ml)	193 ± 14	188 ± 7

† The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats, as determined by Student's t test for group comparisons ($P < 0.01$).

Average Rates of Protein Synthesis in the Brain as a Whole

The mean rates of protein synthesis in the brain as a whole were calculated from the local values of all of the brain structures weighted for their volumes by the image-processing technique of Goochee *et al.* (1980). In comparison with the young adult rats, the weighted average rate of protein synthesis in the older animals was significantly reduced by 17 per cent below that of the young animals (Table 2).

Local Rates of Protein Synthesis

Local rates of protein synthesis were determined in 39 brain structures. For the purpose of presentation these structures have been grouped according to the functional systems with which they are presumed to be associated.

Rates of protein synthesis were determined in the brain structures of three sensory systems. In the auditory system (Table 3) 6 structures were examined. Of these structures rates of protein synthesis were significantly reduced in the older animals

TABLE 2 EFFECTS OF AGEING ON AVERAGE RATE OF PROTEIN SYNTHESIS IN BRAIN AS A WHOLE†

Age group	*Age* *(months)*	*Cerebral protein synthesis* *(nmol leucine incorporated/g tissue/min)*
Young adult (6)	6	4.2 ± 0.1
Middle-aged/aged (12)	15–23	3.5 ± 0.2**

† Values are the means ± standard errors obtained in the number of animals given in parentheses. ** Significantly different from the young adult rats, as determined by Student's t test for group comparisons ($P < 0.005$).

TABLE 3 AUDITORY, VISUAL, AND EXTRAPYRAMIDAL MOTOR SYSTEMS· EFFECTS OF AGEING ON RATES OF PROTEIN SYNTHESIS

	Local cerebral protein synthesis† *(nmol leucine incorporated/g tissue/min)*	
Structure	*Young adult (6 months)*	*Middle-aged/aged (15–23 months)*
Auditory system		
Auditory cortex (cortical area 41)	5.2 ± 0.2 (6)	4.7 ± 0.2 (12)
Medial geniculate body	5.4 ± 0.2 (6)	4.7 ± 0.3 (12)
Inferior colliculus	6.2 ± 0.3 (6)	4.9 ± 0.2*** (12)
Lateral lemniscus, ventral	5.8 ± 0.3 (6)	4.6 ± 0.2** (11)
Superior olivary nucleus	5.2 ± 0.6 (6)	4.4 ± 0.3 (11)
Cochlear nucleus, ventral	6.4 ± 0.4 (6)	5.3 ± 0.3* (10)
Visual system		
Visual cortex (cortical area 17)	5.7 ± 0.2 (6)	4.8 ± 0.2* (12)
Lateral geniculate body	4.8 ± 0.2 (6)	4.1 ± 0.2* (12)
Superior colliculus	4.9 ± 0.2 (6)	4.1 ± 0.2* (12)
Thalamus: posterior lateral nucleus	3.9 ± 0.2 (5)	3.6 ± 0.2 (8)
Extrapyramidal motor system		
Caudate-putamen	3.7 ± 0.2 (6)	3.2 ± 0.2 (12)
Globus pallidus	2.4 ± 0.1 (6)	2.2 ± 0.1 (12)
Substantia nigra (zona compacta)	2.0 ± 0.1 (6)	1.7 ± 0.1* (12)
Inferior olivary nucleus	5.9 ± 0.3 (6)	4.4 ± 0.2*** (10)
Pontine grey matter	3.9 ± 0.2 (6)	3.1 ± 0.2** (12)
Thalamus: ventral nucleus	5.3 ± 0.2 (6)	4.9 ± 0.2 (12)
Vestibular nucleus, superior	7.4 ± 0.3 (6)	6.2 ± 0.3* (12)
Red nucleus	5.2 ± 0.2 (6)	3.9 ± 0.2*** (11)

† Values are the means ± standard errors obtained in the number of animals given in parentheses. Asterisks indicate difference from the young adult rats, as determined by Student's t test for group comparisons: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$.

by between 17 and 21 per cent in the inferior colliculus, lateral lemniscus, and cochlear nucleus. In the visual system (Table 3), rates of protein synthesis in visual cortex (area 17), lateral geniculate nucleus, and superior colliculus were all significantly decreased in the older animals by about 15 per cent. The rate of protein synthesis in the olfactory cortex (cortical area 51) was significantly lower in the older animals by 20 per cent as compared with the young controls (Table 4). In 4 other cortical areas (Table 4), frontal (area 10) and parietal (area 7), sensorimotor (area 2), and cerebellar cortex, rates of protein synthesis were unaltered in the older animals.

Of the 8 structures examined in the extrapyramidal motor system (Table 3), 5 had reduced rates of protein synthesis in the older animals. Some of the largest changes were found in the inferior olivary nucleus and the red nucleus, both of which were decreased by 25 per cent. The rates of protein synthesis in the substantia nigra,

TABLE 4 CORTICAL STRUCTURES AND REGIONS OF WHITE MATTER: EFFECTS OF AGEING ON RATES OF PROTEIN SYNTHESIS

Structure	Local cerebral protein synthesis† (nmol leucine incorporated/g tissue/min) *Young adult (6 months)*	 *Middle-aged/aged (15–23 months)*
Cortical structures		
Parietal cortex (cortical area 7)	5.2 ± 0.2 (6)	4.6 ± 0.2 (12)
Olfactory cortex (cortical area 51)	7.7 ± 0.3 (6)	6.2 ± 0.4* (10)
Frontal cortex (cortical area 10)	5.1 ± 0.2 (6)	4.9 ± 0.2 (12)
Sensorimotor cortex (cortical area 2)	5.2 ± 0.2 (6)	4.7 ± 0.2 (12)
Cerebellar cortex	5.9 ± 0.2 (6)	5.3 ± 0.3 (12)
White matter regions		
Corpus callosum, splenium	2.0 ± 0.1 (6)	1.7 ± 0.1 (12)
Genu of corpus callosum	2.2 ± 0.1 (6)	2.0 ± 0.1 (12)
Internal capsule	2.1 ± 0.1 (6)	1.7 ± 0.1** (12)
Cerebellar white matter	1.7 ± 0.1 (6)	1.4 ± 0.1* (12)

† Values are the means ± standard errors obtained in the number of animals given in parentheses. Asterisks indicate significant difference from the young adult rats, as determined by Student's t test for group comparisons: * $P < 0.05$; ** $P < 0.01$.

TABLE 5 LIMBIC SYSTEM AND OTHER AREAS EFFECTS OF AGEING ON RATES OF PROTEIN SYNTHESIS

Structure	Local cerebral protein synthesis† (nmol leucine incorporated/g tissue/min) *Young adult (6 months)*	 *Middle-aged/aged (15–23 months)*
Hippocampus; CA1	6.5 ± 0.4 (6)	5.5 ± 0.4 (12)
Dentate gyrus, supragranular zone	8.4 ± 0.6 (6)	7.0 ± 0.3* (12)
Amygdala, lateral	5.9 ± 0.3 (6)	5.0 ± 0.3 (12)
Septal nucleus, lateral	3.9 ± 0.3 (6)	3.6 ± 0.2 (12)
Nucleus accumbens, medial	3.9 ± 0.3 (6)	3.1 ± 0.2* (9)
Habenula	11.0 ± 0.8 (4)	9.2 ± 0.9 (9)
Interpeduncular nucleus	5.5 ± 0.3 (6)	5.0 ± 0.2 (12)
Locus coeruleus	7.6 ± 0.4 (6)	5.9 ± 0.4** (10)
Hypothalamus:		
Ventral medial	5.4 ± 0.4 (6)	4.9 ± 0.4 (7)
Paraventricular	11.5 ± 0.6 (6)	10.0 ± 0.7 (8)
Supraoptic	12.0 ± 1.0 (4)	11.8 ± 1.2 (7)
Mamillary body	4.9 ± 0.2 (6)	4.8 ± 0.3 (12)

† Values are the means ± standard errors obtained in the number of animals given in parentheses. Asterisks indicate significant difference from the young adult rats, as determined by Student's t test for group comparisons. * $P < 0.05$; ** $P < 0.01$.

vestibular nucleus, and pontine grey matter were also significantly reduced in the aged animals.

In the limbic system (Table 5), only the dentate gyrus and the nucleus accumbens were affected in the older animals. The rate of protein synthesis in the locus coeruleus (Table 5) was very significantly decreased by 22 per cent in the older group. In the 4 white matter structures examined, the internal capsule and cerebellar white matter were significantly affected in the older animals (Table 4).

DISCUSSION

The results of these studies demonstrate that in the normal Sprague-Dawley rat, ageing is associated with decreases in the rates of protein synthesis in the brain as a whole and in some specific brain regions. The regional changes are clearly selective and show a predilection for certain neural systems. Specifically, sensory and extrapyramidal motor systems are particularly affected whereas most areas of cortex and regions involved in higher functions are spared. When the results of the present studies are compared with those of a previous study (Smith *et al.*, 1980*b*) on the effects of ageing in Sprague-Dawley rats on local rates of cerebral glucose utilization (Table 6), it is apparent that structures of the visual and auditory systems are affected with respect to both biochemical processes throughout the entire extent of their respective pathways. On the other hand, the only significant age-related effects on glucose utilization outside the auditory and visual systems are in the caudate-putamen and white matter structures, whereas senescent decreases in protein synthesis are found in several structures of the limbic system, four regions involved in motor function, several white matter structures, the locus coeruleus, and pontine grey matter.

The decreases in glucose utilization in the visual and auditory systems may reflect a partial deafferentation due to retinal degeneration (Schardein *et al.*, 1975; Lai *et al.*, 1978) and degenerative changes in the organ of Corti. An acute decrease in visual or auditory input results in marked reductions in glucose consumption in components of the visual or auditory systems, respectively (Kennedy *et al.*, 1975; Sokoloff, 1977). The consequences of chronic decreases in sensory input are, however, still unknown. Glucose consumption, which is so closely linked to functional activity, would presumably remain reduced but, in addition, involutional changes in the brain structures involved in sensory function might result. Whether the senescent decreases found in glucose utilization in structures of the visual and auditory systems are related to such involutional changes or merely to a lack of input could not be distinguished on the basis of the studies on regional glucose utilization. The results of the present studies, in which decreased rates of protein synthesis were found in visual and auditory structures in the aged animals, suggest that there has been some involution in both of these systems. Because protein synthesis is a process necessary for long-term maintenance and remodelling in the nervous system and is less reflective of immediate functional activity, it may more nearly reflect the

TABLE 6 COMPARISON OF EFFECTS OF AGEING ON LOCAL RATES OF CEREBRAL GLUCOSE UTILIZATION AND PROTEIN SYNTHESIS

	Glucose utilization†		*Protein synthesis*	
Structure	*Significance*	*Percentage change*	*Significance*	*Percentage change*
Visual system				
Visual cortex (area 17)	***	−22	*	−16
Lateral geniculate	*	−18	*	−15
Superior colliculus	***	−17	*	−16
Thalamus, posterior lateral nucleus	*	−14	n.s.	
Auditory system				
Auditory cortex (area 41)	n.s.		n.s.	
Medial geniculate	***	−18	n.s.	
Inferior colliculus	**	−16	***	−21
Lateral lemniscus, ventral	**	−16	**	−21
Superior olivary nucleus	**	−16	n.s.	
Cochlear nucleus	n.s.		*	−17
Other cortical regions				
Olfactory cortex (area 51)	n.s.		*	−19
Parietal cortex (area 7)	n.s.		n.s.	
Frontal cortex (area 10)	n.s.		n.s.	
Sensorimotor cortex (area 2)	n.s.		n.s.	
Cerebellar cortex	n.s.		n.s.	
Limbic system and related structures				
Hippocampus: CA1	n.d.		n.s.	
CA2	n.s.		n.d.	
CA3	n.s.		n.d.	
Dentate gyrus, supragranular zone	n.s.		*	−17
Lateral amygdala	n.d.		n.s.	
Medial amygdala	n.s.		n.d.	
Lateral septal nucleus	n.s.		n.s.	
Nucleus accumbens	n.s.		*	−21
Habenula	n.d.		n.s.	
Interpenduncular nucleus	n.s.		n.s.	
Locus coeruleus	n.d.		**	−22
Hypothalamus: Ventral medial	n.s.		n.s.	
Paraventricular	n.d.		n.s.	
Supraoptic	n.d.		n.s.	
Mamillary body	n.s.		n.s.	

† Derived from data of Smith *et al.* (1980*b*). Values for the middle-aged and aged groups were combined to form a middle-aged/aged group equivalent to that used in the present study of protein synthesis. Asterisks indicate significant difference between the young adult and the middle-aged/aged rats as determined by Student's t test for group comparisons: n.s. = not significant; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; n.d. = not determined.

	Glucose utilization†		*Protein synthesis*	
Structure	*Significance*	*Percentage change*	*Significance*	*Percentage change*
Extrapyramidal motor system				
Caudate putamen	***	−16	n.s.	
Globus pallidus	n.s.		n.s.	
Substantia nigra (zc)	n.s.		*	−15
Inferior olivary nucleus	n.s.		***	−25
Pontine grey matter	n.s.		**	−21
Thalamus, ventral nucleus	n.s.		n.s.	
Red nucleus	n.d.		***	−25
Superior vestibular nucleus	n.s.		*	−16
White matter structures				
Splenium corpus callosum	*	−26	n.s.	
Genu of corpus callosum	n.s.		n.s.	
Internal capsule	*	−24	**	−19
Cerebellar white matter	***	−27	*	−18

structural and functional capacity of the nervous system. In the visual and auditory systems, at least, the changes in protein synthesis and glucose utilization may both indicate a retrogressive response in these structures to a chronic lack of input. The loss of pyramidal cell dendritic spines and branches found in both the visual (Feldman, 1976) and auditory (Vaughan, 1977) cortex of aged rats supports this idea.

Cortical areas, other than primary sensory areas, and structures of the limbic system, were generally unaffected by ageing (Table 6) with respect to either glucose utilization or protein synthesis. The significantly decreased rate of protein synthesis found in the supragranular zone of the dentate gyrus may be related to the reported senescent losses of synaptic terminals and dendrites in this area (Geinisman *et al.*, 1977, 1978). The decreased protein synthesis in the nucleus accumbens is of particular interest because of the mounting evidence that this nucleus has a significant role in mediating locomotor behaviour *via* a dopaminergic pathway (Pijenenburg and van Rossum, 1973; Jackson *et al.*, 1975; Kelly *et al.*, 1975, 1982) and that mesotelencephalic dopaminergic motor pathways are affected by the ageing process (reviewed by Finch *et al.*, 1981).

The nigrostriatal dopaminergic system is particularly affected by the ageing process. In the present study a decreased rate of protein synthesis was found in the zona compacta of the substantia nigra in the old rats. The evidence that this pathway is affected with age is considerable. Clinically, human aged show an increased incidence of parkinsonian signs (Critchley, 1956) and of extrapyramidal side effects to neuroleptic drugs (Crane, 1974). In aged rats, it has been observed (Marshall and Berrios, 1979) that there are deficits in swimming behaviour which are diminished by the administration of apomorphine. Other studies (Gage *et al.*, 1983) of aged rats have shown that intrastriatal dopaminergic grafts are associated with significant improvement in the scores on some tests of motor coordination. In a number of species decreases with age in dopamine turnover (Finch, 1973), number of dopamine receptors (Makman *et al.*, 1979; Severson and Finch, 1980; Severson *et al.*, 1982), and dopamine-sensitive adenylcyclase (Govoni *et al.*, 1977; Puri and Volicer, 1977) in the striatum are well documented. In the study of the effects of ageing on local rates of glucose utilization (Smith *et al.*, 1980*b*) significant decreases were found in the caudate-putamen (Table 6). Of the many senescent changes that have been found in the striatum, most involve the dopaminergic terminals so rich in this area. Protein synthesis is unchanged in this region (Table 4), but it is significantly decreased in the substantia nigra where the cell bodies of origin of the striatal dopaminergic terminals are located.

Apart from a significant decrease in glucose utilization in the caudate putamen, there are no effects of ageing on glucose utilization in motor areas (Table 6). In contrast, protein synthesis rates are decreased in the older animals in many regions involved in motor function (Tables 4 and 6), particularly in the red nucleus and the inferior olivary nucleus. It is possible that these effects are related to more general effects on the extrapyramidal motor system inasmuch as well-defined neuronal circuits exist between the striatum and cerebellum *via* the inferior olivary nucleus (Fox and Williams, 1970) and between the red nucleus and inferior olivary nucleus (Walberg, 1956).

There may also be effects of ageing on noradrenergic pathways. The rate of protein synthesis was significantly reduced in the locus coeruleus in the old animals (Table 5). The locus coeruleus contains the cell bodies of origin of the major ascending noradrenergic innervation of the basal telencephalon and the entire isocortex. The effect of age on glucose utilization in the locus coeruleus was not determined in the previous study of senescent changes in energy metabolism (Smith *et al.*, 1980*b*); a further examination of both glucose utilization and protein synthesis in this region and other catecholaminergic nuclei and their projection sites is warranted.

The present studies utilize a quantitative autoradiographic method to measure local rates of cerebral protein synthesis that is still being refined (Smith *et al.*, 1980*a*, 1984). The details of its development and validation will be published separately. Briefly, the kinetic model for the behaviour of leucine in brain used in formulating the operational equation (fig. 1) assumes a single free leucine precursor pool for protein synthesis that exchanges with plasma but with no admixture of leucine derived from protein degradation. Although this model is probably oversimplified, it is likely to be adequate for the present studies for the following reasons. There are two major requirements for a method of this type: (1) a means of determining the amount of labelled product formed (the numerator of the operational equation (fig. 1)), and (2) a means of determining the integrated specific activity of the precursor pool for the reaction (the denominator of the operational equation (fig. 1)). The total amount of ^{14}C in the tissue at the end of the experiment, Ci*, is determined by quantitative autoradiography; it represents the combined concentrations of [^{14}C]leucine incorporated into protein (i.e. product) and residual free [^{14}C]leucine remaining in the tissue represented by the second term in the numerator. As calculated with the equation this second term equals 2 to 5 per cent of the Ci* at 60 min after the pulse. Also, acid-soluble ^{14}C, which includes free [^{14}C]leucine and α-[^{14}C]ketoisocaproic acid, if any, has been measured experimentally and found to be approximately 5 per cent of the Ci* 60 min after the pulse of [1-^{14}C]leucine. The correction of Ci* for free [^{14}C]leucine is, therefore, an almost minimal source of error in the rat. The integrated specific activity of the precursor pool is calculated from the history of the plasma specific activity (first term in denominator) and the lag between the plasma and the precursor pool in the tissue (corrected for in the second term in denominator). The half-life of the precursor pool has been estimated in a separate series of experiments to be less than 3.5 min. With a pool turning over at such a rapid rate the difference between its integrated specific activity and that of the plasma will be relatively small 30 to 60 min after a pulse of [^{14}C]leucine, and correction for the lag is almost negligible.

The assumption that there is no admixture of leucine derived from protein degradation with the precursor pool is one for which there is evidence derived from *in vitro* experiments (Gainer *et al.*, 1975; Robertson and Wheatley, 1979). Such admixture, if present, would dilute and, therefore, reduce the precursor pool specific activity because it would provide a source of constant dilution of the radioactive amino acid entering the precursor pool from the plasma. Experiments are currently in progress to assess the degree of admixture but, in the meantime the rates of protein synthesis in the present studies were calculated with the assumption that the admixture is negligible. If there is, indeed, significant admixture, then the data presented here represent the minimal rather than the actual rates of leucine incorporation into protein.

The design of the leucine method which utilizes a pulse injection followed by a 60 min interval for clearance of free [^{14}C]leucine from the brain minimizes possible artefacts due to differences in blood flow and amino acid transport. It does not rule out the possibility, however, that in extreme conditions blood flow or transport could be limiting the rate of protein synthesis. The results of studies with the leucine method show changes in the rate of protein synthesis, but they do not demonstrate the cause of the changes.

The finding of decreases in brain protein synthesis with age agrees well with ideas of the involutional nature of the ageing process. Of particular interest in the present study is the finding that changes in protein synthesis are regionally selective. A decreased rate of protein synthesis in a brain region may reflect either a decrease in the number of cells or an atrophy of existing cells in the region. Either neurons or glial cells could be affected. In the case of neurons, an atrophy of the terminal regions might be reflected in decreased rates of protein synthesis in the cell bodies of origin. The findings of senescent decreases in protein synthesis in substantia nigra, inferior olivary nucleus, and locus coeruleus are of interest in light of studies of the effects of ageing on neuron number in these regions (Monagle and Brody, 1974; McGeer *et al.*, 1977; Vijayashankar and Brody, 1979; Goldman and Coleman, 1981). In regions in which neuron number does not appear to change significantly with age decreases in protein synthesis may indicate that the extent of the terminal fields of these neurons has decreased or, alternatively, changes may have occurred in glial cells.

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(*Received May 22, 1984. Revised August 20, 1984 Accepted August 30, 1984*)

Brain (1985) **108**, 171-191

THE EFFECTS OF L-DOPA ON REGIONAL CEREBRAL BLOOD FLOW AND OXYGEN METABOLISM IN PATIENTS WITH PARKINSON'S DISEASE

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SUMMARY

Studies performed on 18 patients with Parkinson's disease and 6 control subjects have shown that acute administration of L-DOPA in clinically effective doses gives rise to a diffuse increase in regional cerebral blood flow without accompanying stimulation of regional oxygen utilization. The data suggest that this rise in rCBF is caused by vasodilatation due to a direct action of the drug on the cerebral blood vessels. The effect of L-DOPA on rCBF did not correlate with the degree of clinical improvement seen in each patient after treatment. The therapeutic effect of L-DOPA in the brain was not reflected in any change of regional cerebral oxygen utilization as measured by our technique. We suggest that the pharmacological actions of L-DOPA in the brain take place on at least two different levels.

INTRODUCTION

L-DOPA is well known for its clinical effects in patients with Parkinson's disease. Much work has been done to clarify its pharmacology (Calne *et al.*, 1969; Morris, 1978) and biochemistry in the brain (Lloyd *et al.*, 1975; Moskowitz and Wurtman, 1975; Hornykiewicz, 1982). These studies indicate that L-DOPA is concentrated and used by striatal neural elements to form dopamine. The structures which are affected by the dopamine-sensitive efferent system of both normals and parkinsonian patients remain to be determined.

The distribution of regional cerebral blood flow (rCBF) and regional oxygen metabolism (rCMRO$_2$) is related to neuronal and synaptic functional activity. Positron emission tomography (PET) provides the opportunity to make regional measurements of rCBF and rCMRO$_2$. Experimental studies in the rat have shown that systemic administration of apomorphine or L-DOPA increases glucose utilization in the basal ganglia and in some related nuclei (Brown and Wolfson,

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1978; McCulloch, Savaki, *et al.*, 1982; Warner *et al.*, 1982; Grome and McCulloch, 1983). Dopamine injected locally into the striatum gives rise to a specific pattern of increased glucose utilization in the projection nuclei (Brown and Wolfson, 1983). On the other hand, a direct action of dopamine on the cerebral vasculature in the cat, *in vitro* and *in vivo*, has deen demonstrated by Edvinsson *et al.* (1978). L-DOPA, dopamine and apomorphine have been shown to influence cerebral blood flow in dogs and rats (Ekström-Jodal *et al.*, 1974; von Essen, 1974; Jauzac *et al.*, 1982; Ingvar *et al.*, 1983). The dopaminergic agonist piribedil also tends to increase cerebral blood flow, both in animals and in man (McCulloch and Edvinsson, 1980; Güell *et al.*, 1982). Bès *et al.* (1983) have found in a group of patients with Parkinson's disease an increase of CBF, particularly in the frontal regions, after administration of bromocriptine.

Recently the relationship between the dopamine-induced increases of local cerebral metabolism and blood flow has been stressed, the former being assumed to be the cause of the latter (McCulloch and Edvinsson, 1980; McCulloch, Kelly and Ford, 1982). However, at least one study suggests that there are only small changes

TABLE 1 CLINICAL DATA OF THE PARKINSONIAN PATIENTS

*Case No.***	*Sex*	*Age (yrs)*	*Duration of disease (yrs)*	*Admitted to hospital*	*Disability score* (off medication)*	*L-DOPA dose (mg) between scans*
1	F	59	4	Yes	445	750
2	M	45	4	Yes	390	500
3	M	72	6	Yes	445	400
4	F	71	3	No	665	375
5	M	66	1	No	160	375
6	M	51	1	No	185	500
7	F	44	3	Yes	510	600
8	F	75	7	Yes	600	375
9	M	62	14	Yes	1080	400
10	M	61	10	Yes	935	600
11	M	60	10	Yes	1305	1000
12	M	62	2.5	Yes	575	750
13	F	75	1	Yes	745	500
14	M	57	5	No	575	500
15	M	51	2	No	170	500
16	M	60	12	Yes	1410	300
17	F	66	5	Yes	895	400
18	M	80	10	Yes	815	750
Mean		62.1	5.6		661	532
± SD		± 10.2	± 4.0		± 363	± 181

*The range of the score is 0–1500 (without the section assessing dyskinetic movements and without the section in which the patients assess their own disability). **Case Nos. 1–6 are predominantly unilaterally and Nos. 7–18 bilaterally affected (*see text*).

in brain metabolism as compared with the alterations in rCBF (Ingvar *et al.*, 1983). We have measured regional cerebral blood flow (rCBF) and oxygen utilization (rCMRO$_2$) in patients with Parkinson's disease and in nonparkinsonian subjects using PET. Both groups of subjects were studied before and after administration of L-DOPA. In particular we hoped to establish whether administration of L-DOPA produces any measureable change of regional cerebral blood flow and oxygen metabolism and if so, whether such changes correlate with the clinical response.

MATERIAL

Eighteen patients with Parkinson's disease were selected from a routine neurological outpatient clinic. They were all self-supporting at home and taking some form of antiparkinsonian drug treatment. In most cases this was L-DOPA with carbidopa. Some patients were also taking bromocriptine and/or benzhexol. Three patients were newly diagnosed and had never been treated with antiparkinsonian medication before. A general physical examination, blood tests and a CT scan were performed to exclude other general or neurological diseases. A Blessed score was used to ensure that no severe dementia was present (Blessed *et al.*, 1968). To assess the clinical disability resulting from their Parkinson's disease, the patients were scored semiquantitatively according to the New York University (NYU) score (Lieberman *et al.*, 1980) at several stages during the study. The section of the NYU score in which subjective disability is graded by the patients themselves was omitted. Six patients (Cases 1-6) had predominantly unilateral symptoms and signs: the disability on the more affected body side was at least three times as severe as on the opposite side according to the NYU score.

Before the patients had their first PET scan their antiparkinsonian medication was discontinued for five days. Most of the patients had to be admitted to hospital during this time because clinical deterioration made inpatient care advisable. The patients (Cases 5, 12 and 15) who had never previously been treated with L-DOPA were first given a ten day trial period of L-DOPA treatment to check that they were able to tolerate the drug. At least two weeks elapsed between the last day of this test treatment and the first PET scan. The patient data are summarized in Table 1.

Control Population

Six volunteers, most of them spouses of the parkinsonian patients, were included as controls (Table 2). The general clinical assessment was the same as for the patients except that routine CT scans were not done.

TABLE 2 CLINICAL DATA OF THE CONTROL SUBJECTS

Case No.	*Sex*	*Age (yrs)*	*L-DOPA dose (mg) between scans*
1	M	41	750
2	M	72	500
3	F	53	250
4	F	63	500
5	F	47	375
6	M	40	750
Mean		52.7	521
±SD		±12.7	±200

Before the volunteers underwent the PET study they were given L-DOPA and carbidopa in gradually increasing doses for ten days, up to a maximum of 500 mg L-DOPA daily, to ensure that they would be able to tolerate the drug. No significant side effects were noted, although 2 volunteers experienced transient nausea. As in the patient group, at least two weeks were interposed between the end of the test period of drug treatment and the baseline PET scan.

The project was approved by the Research Ethics Committee of the Hammersmith Hospital and permission for use of the appropriate isotopes was obtained from the UK Administration of Radioactive Substances Advisory Committee. All patients and volunteers gave their written informed consent.

METHODS

Scanning Procedure

The patients and controls were scanned in the ECAT-11 (E.G and G. Ortec, Oak Ridge, Tennessee) positron emission tomograph. This is a single slice machine with a hexagonal array of NaI detectors capable of determining the concentration of positron emitting radioisotopes quantitatively within a volume of tissue. The spatial resolution is 16.7 x 16.7 mm (full width half maximum) in the transaxial plane and the slice thickness is 16 mm (Phelps *et al.*, 1978).

The total duration of the scanning procedure was between 1.5 and 2 h. Each subject was scanned in two tomographic planes, the first through the cerebellum, 2.5 cm above the orbitomeatal (OM) line, and the second 4.5 cm above the OM line at the level of the basal ganglia. The position of the head was maintained precisely by the use of a grid of light projected on the forehead of the subject. Prior to the scanning procedure, a short radial artery cannula (Teflon, 21 gauge) was inserted to allow serial arterial blood sampling during the scan. The isotope activity in each sample was measured in a well-counter, cross-calibrated with the tomograph. Twice during each scanning procedure the arterial blood gases, pH, haemoglobin and haematocrit were measured, and from these the total arterial oxygen content was calculated. In total about 50 ml of blood was taken during each scanning procedure.

Steady State Inhalational Technique

The positron emitting isotope used for both cerebral blood flow (CBF) and oxygen extraction ratio (OER) measurements is ^{15}O, which has a short half life of 123 s and is produced continuously by a cyclotron throughout the scanning procedure. The $C^{15}O_2$ and $^{15}O_2$ are delivered from the cyclotron at a constant flow of 0.5 L/min in concentrations of 20 and 60 μCi/ml, respectively. These gaseous isotopes are administered sequentially, being inhaled continuously by the subjects *via* a small plastic mask. After a period of about 5 times the half life of the isotope (approximately 10 min) an equilibrium is reached between the input of the isotope into the brain tissue and the output, which is determined by blood flow washout from the tissue and decay of the isotope. Adequacy of the steady state is checked by the integrated response during the scans and confirmed afterwards from the uniformity of activity in the serial arterial blood samples.

When $C^{15}O_2$ is inhaled the ^{15}O is transferred in the capillary bed of the lungs to become incorporated into water ($H_2{}^{15}O$). Continuous inhalation of $C^{15}O_2$ therefore results in a constant arterial supply of $H_2{}^{15}O$ to the peripheral tissues. As water is freely diffusible in tissue the amount of $H_2{}^{15}O$ in a certain volume of brain relates directly to the regional cerebral blood flow (rCBF). During inhalation of ^{15}O-labelled molecular oxygen ($^{15}O_2$), the ^{15}O becomes bound to haemoglobin and is subsequently extracted by the cells in the tissue. Relating the data from the $^{15}O_2$ to the blood flow data the regional oxygen extraction ratio (rOER) can be calculated. The regional cerebral metabolic rate of oxygen ($rCMRO_2$) is then calculated as follows: $rCMRO_2 = rCBF \times rOER \times$ total stable oxygen content of the arterial blood.

The tracer model and its theoretical and statistical validation have been described in detail elsewhere

(Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981; Lammertsma *et al.*, 1982). Also, examples of its application to the study of dementia and stroke have previously been published (Frackowiak *et al.*, 1981; Wise *et al.*, 1983). Following data collection the tomographic brain sections are produced using standard reconstruction techniques.

Methods of Analysis

On the computer video display unit, regions of interest (ROI) were defined in the basal ganglia territories, cerebellum and cortical regions. Corresponding values for rCBF, rOER and rCMRO$_2$ were taken from these standardized regions in each subject.

Data from these locations in the basal ganglia territories in each hemisphere were averaged and taken as a value for the basal ganglia. The ROI was ovoid in shape with a horizontal and vertical radius of 4 pixels comprising a total area of 41 pixels (one pixel is 2.5 mm × 2.5 mm). The anatomical localization of the basal ganglia ROI was defined by a standardized procedure based on careful reference to the CT scans, which were taken parallel to the OM line in the same planes as the PET scans. The distances of the heads of the caudate nucleus relative to the frontal and occipital poles of the brain and relative to the midline were determined on the CT scans of the patients and superimposed on the PET scans. As the relative distances were virtually identical in all patients, we have used the same ratios for the control subjects.

The ROIs in the cerebellum were defined in each cerebellar hemisphere as the 41 pixel area with highest mean blood flow which had the lowest standard deviation. The cortical areas in the emission scans were selected by taking blocks of 3 × 6 pixels around the peak values at the edge of the scans. A detailed description of the procedure to select cortical samples is given by Wise *et al.* (1983). Four contiguous blocks constituted one cortical sample. From the cortex of each hemisphere one frontal, one temporal and one occipital ROI was chosen. The average of these three samples was taken as the cortical value for that hemisphere.

Mean values from the cortical and basal ganglia ROIs were determined for each cerebral hemisphere. The values quoted below as 'cortical', 'basal ganglia' and 'cerebellar' represent the average from both sides of the brain. Paired t tests were used to compare the values of rCBF, rOER and rCMRO$_2$ in the corresponding brain territories before and after administration of L-DOPA.

Sequence of Scans and Clinical Assessments

Immediately before the baseline scan the clinical disability of the patients was scored as described above and a premedication of 75 mg carbidopa was given orally to each subject. The duration of the baseline scanning procedure was 1.5–2 h. Immediately after this a single oral dose of L-DOPA and carbidopa was given. The dose of L-DOPA given to the patients ranged from 300 mg to 1250 mg, depending on the amount of L-DOPA the patients were previously taking on a daily basis to achieve a clinically satisfactory state. Thus by administering corresponding doses in our study we made sure that the patients would show a clear clinical response. The control subjects received 250 to 750 mg L-DOPA, depending on whether they had noted any nausea while taking the drug during the test trial before entering the study (*see above*). One hour after administration of the L-DOPA the clinical disability score was repeated and the second scanning procedure was performed in exactly the same way as the baseline scan. During the second scan, two additional arterial blood samples were taken to measure the plasma L-DOPA concentration. This was carried out by high performance liquid chromatography with amperometric detection, a procedure which has recently been described in a separate paper (Causon *et al.*, 1983). After the second scan the patients were restarted on their original medication and discharged from hospital. Those patients who had never previously been treated were started on a continuous drug regimen with L-DOPA, increasing the dose until an optimal clinical condition was reached. In 11 of the 14 patients who had acute L-DOPA studies it was possible to perform a third scan 2 to 4 weeks later at a time when their regular optimal L-DOPA treatment had been reestablished. The clinical disability score was repeated on that occasion.

The blood pressure and pulse rate were measured three times during each scanning procedure and the mean blood pressure was calculated as the diastolic blood pressure plus one-third of the difference between systolic and diastolic pressure.

In four studies (Cases 6 and 14; control subjects 2 and 3) additional CO_2 scans were performed during the post L-DOPA procedure to see whether the rCBF changed acutely in the course of 60 min and if so, whether these changes related to the plasma L-DOPA level.

RESULTS

A total of 54 technically adequate scans were carried out: 24 baseline scans (18 patients, 6 normals), 19 scans 1 h after L-DOPA (14 patients, 5 normals) and 11 scans (only patients) several weeks after continuous L-DOPA treatment.

In 5 studies it was not possible to scan following the acute L-DOPA administration. Two of these failures resulted from cyclotron breakdowns and two patients and one control subject were unable to continue because of nausea and vomiting after receiving the drug.

Fig. 1 shows the clinical response to L-DOPA 1 h after oral administration of the drug. Almost all patients showed marked improvement, although there was quite wide variation between individuals. The mean disability score decreased from 661 (SD ± 363) to 303 (SD ± 268) and after several weeks of continuous drug treatment was 318 (SD ± 228). The acute change following L-DOPA was highly significant

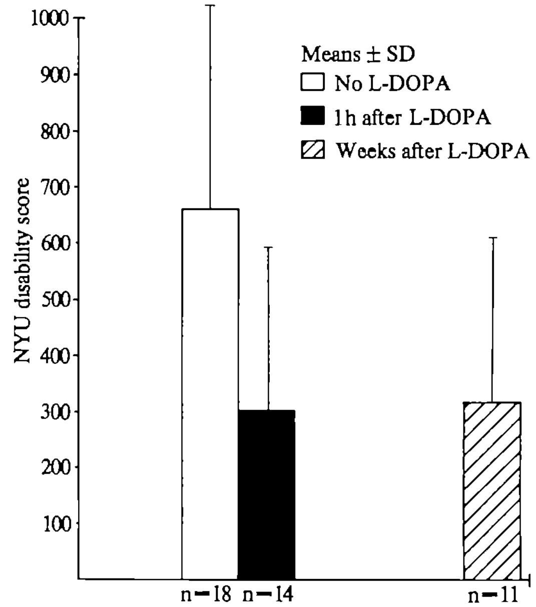

FIG. 1. The clinical disability of the patients as measured with the New York University (NYU) disability score before and after treatment with L-DOPA in combination with carbidopa.

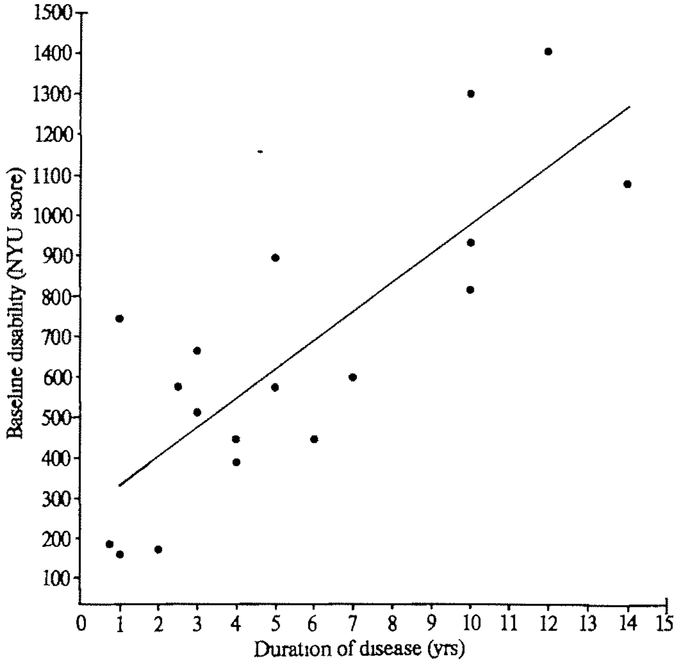

FIG. 2. The relationship between the degree of clinical disability (New York University disability score) and the duration of the disease in the group of patients with Parkinson's disease The disability was assessed when the patients were without treatment.

($P < 0.0001$). As shown in fig. 2, there was a reasonably good correlation between the baseline disability score and the duration of the disease ($r = 0.65$, $P < 0.005$). Most of the patients showed rest tremor while lying on the couch during the baseline scan. This tremor had disappeared in all cases during the second scan performed 1 h after oral administration of L-DOPA.

The plasma L-DOPA level (Table 3) was widely variable between individuals. However, the dose of L-DOPA expressed in mg/kg body weight correlated reasonably well with the plasma L-DOPA level ($r = 0.65$, $P < 0.01$). No correlation could be found between the plasma L-DOPA level and the clinical improvement expressed as the percentage difference in disability score before and after L-DOPA administration. In contrast there was a relationship between the plasma level and the incidence of side effects (i.e. vomiting, nausea and dyskinesia). Only those patients with a plasma level above 3.0 μg/ml developed dyskinesias, the higher levels being associated with more severe dyskinesias. No dyskinesias were present in the baseline condition. The 2 patients who vomited and were excluded from further study were also those in the group with the highest plasma levels. The control subjects had no dyskinesias. However, their plasma levels were lower than in

TABLE 3 PLASMA L-DOPA LEVELS AND CLINICAL SIDE EFFECTS

Subjects	*L-DOPA dose (mg/kg)*	*Plasma L-DOPA μg/ml*	*Dyskinesia after L-DOPA*	*Nausea/ vomiting*
Patients				
1	13.7	4.20	+++	—
2	—	2.93	—	—
3	9.0	3.55	—	—
4	8.6	2.80	—	—
5	5.2	1.96	—	—
6	5.3	1.10	—	—
7	13.4	—	—	—
8	—	—	—	++
9	5.8	2.70	—	—
10	7.5	3.86	++	—
11	13.3	3.19	+	—
12	9.8	4.00	+++	—
13	9.3	2.20	—	—
14	—	2.60	—	—
15	5.9	2.10	—	—
16	4.9	3.08	+	—
17	8.4	3.80	*	+++
18	11.7	4.65	*	+++
Mean	8.8	3.05		
±SD	±3.1	±0.94		
Control subjects				
1	9.7	3.54	—	—
2	7.0	2.15	—	—
3	4.1	1.96	—	—
4	8.7	1.46	—	—
5	6.6	1.50	—	—
6	10.3	1.79	*	++++
Mean	7.7	2.07		
±SD	±2.3	±0.77		

*These subjects could not be assessed properly because of nausea and vomiting.

the patients, due to a lower dose of L-DOPA per kg body weight. The subject who received the highest dose per kg body weight was extremely nauseated but had a surprisingly low plasma L-DOPA level.

There were no differences in mean blood pressure (MBP) and mean pulse rate measurements during the scanning procedures before and after L-DOPA administration. There was a slight increase in mean arterial $paCO_2$, both in the control subjects and in the patients, with mean percentage rises of 5.1% ($P < 0.04$) and 3.8% ($P < 0.01$), respectively.

TABLE 4. REGIONAL CEREBRAL BLOOD FLOW (rCBF)

				Scans after L-DOPA					
	Baseline scan			*After 1 h*			*After weeks*		
Patient No **	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*
1	39 2	38 7	47 5	41 2	49 8	51 0	41 2	42 0	47 0
2	37.3	38.3	43 5	44 0	46.5	37 0	—	—	—
3	35 8	40 8	—	44 5	43.2	—	39 7	42.5	—
4	49.0	54 8	—	56 0	70 3	—	—	—	—
5	40 0	43 3	—	35.0	38 0	—	31 5	38 7	—
6	39.2	37.7	52 5	39 7	46.3	57.0	—	—	—
7	43 3	34 5	46 5	59 5	57 7	49 5	40 8	36.7	34 0
8	36.0	35 3	—	41 0	40 8	—	—	—	—
9	36.8	32.8	45.5	40 0	37 7	32 0	35 2	30 0	50 5
10	34 7	33 8	36 5	43 5	40 2	44 0	46.8	53.7	38 0
11	40 5	42 3	38 5	43 7	45 5	33 5	45 8	44 0	24 5
12	31.3	26.2	31.0	36 8	30 7	31 5	34 0	36 0	37.0
13	32 0	24 8	44 5	32 3	33 3	42 0	37.3	28.5	37 0
14	34.2	31 2	46 0	40 7	34 7	39.5	—	—	—
15	52 3	52.5	40 0	—	—	—	44.7	41.8	41 0
16	32 0	38.3	40 0	—	—	—	44 0	49.2	38 5
17	36 5	35 0	31 0	—	—	—	—	—	—
18	38.2	35 7	54 5	—	—	—	—	—	—
	n = 18	n = 18	n = 14	n = 14	n = 14	n = 10	n = 11	n = 11	n = 9
Mean	38 2	37 6	42 7	42 7	43 9	41 7	40 1	40 3	38 6
±SD	±5.5	±7 6	±7 0	±7 3	±10 4	±8 7	5 1	±7 5	±7 4
Control subjects									
1	42.5	33.7	42 5	49.5	53.7	64 5	—	—	—
2	34.0	31 8	52 0	54 7	37 5	38 0	—	—	—
3	43 2	36 3	48 0	43.3	40 7	46 5	—	—	—
4	50 5	49.8	55.5	57 0	56.5	47.5	—	—	—
5	48.7	53 0	58 0	46 0	45 3	56 5	—	—	—
6	39 5	42 3	38 5	—	—	—	—	—	—
	n = 6	n = 6	n = 6	n = 5	n = 5	n = 5	—	—	—
Mean	43 1	41 2	49 1	50 1	46 7	50 6	—	—	—
±SD	±6 0	±8 8	±7.6	±5 7	±8.2	±10 2	—	—	—

*Basal ganglia region. **Patients 1–6 are predominantly unilaterally and 7–18 bilaterally affected (*see text*)

In Tables 4, 5 and 6 the rCBF, rOER and rCMRO$_2$ values of the 'cortex', 'basal ganglia' and 'cerebellum' regions for each individual are shown. The scan at the level of the cerebellum was not carried out in 4 of the patients. The mean values and standard deviations for each group of results are shown in fig. 3. The mean percentage differences for each group are listed in Table 7.

Baseline Comparisons between Patients and Control Subjects of rCBF, rOER and rCMRO$_2$

The baseline values for rCBF and rCMRO$_2$ were higher in the control population than in the patients, whereas the rOER was virtually identical in the two groups. The cortical values were similar to those in the basal ganglia regions, although the latter had slightly lower values for rCBF (mean difference 2.1% in patients, 4.7% in control subjects) and rCMRO$_2$ (mean difference 2.7% in patients, 5.4% in control subjects). This was probably because of a relative underestimation of values in the basal ganglia region due to a partial volume effect, the importance of which has been extensively shown by Mazziotta *et al.* (1981). The values in the cerebellum were higher than those in the cortical regions both in control subjects and in patients. The percentage oxygen extraction (rOER), however, was remarkably similar in all regions in all groups.

The frontal cortical values were lower compared to the more posterior values both in control subjects and in the patients for rCBF and $rCMRO_2$.

Effects of L-DOPA on rCBF, $rCMRO_2$ and rOER

Patient group. After administration of L-DOPA there was with one exception (Case 5) an increase of rCBF in both the cortical and basal ganglia regions, but not in the cerebellum. The change of rCBF in the cortical regions ranged from -12.5 to $+37.3\%$ (mean $+13.0\%$, $P < 0.003$) and in the basal ganglia region from -12.3 to $+67.2\%$ (mean $+20.1\%$, $P < 0.001$). The absolute increase in rCBF in the frontal regions was similar to the increase in the posterior regions (data not shown). The

TABLE 5 REGIONAL OXYGEN EXTRACTION RATIO (rOER)

				Scans after L-DOPA					
	Baseline scan			*After 1 h*			*After weeks*		
Patient No **	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*
1	52.5	51.5	52.5	43.5	41.8	43.0	49.2	48.7	44.0
2	49.0	47.8	43.0	42.2	40.2	47.0	—	—	—
3	56.7	50.0	—	49.2	47.5	—	56.0	54.5	—
4	42.8	44.7	—	39.7	34.7	—	—	—	—
5	44.3	44.3	—	45.3	43.4	—	54.3	47.2	—
6	49.0	48.3	48.5	43.0	38.8	44.0	—	—	—
7	53.7	52.0	66.0	43.3	37.0	42.5	49.3	50.2	53.0
8	56.0	54.8	—	46.2	45.0	—	—	—	—
9	44.7	47.0	44.5	43.5	32.5	53.5	47.5	48.7	44.5
10	50.7	43.5	46.5	37.0	38.7	41.0	42.0	38.2	47.5
11	50.2	47.8	43.5	43.2	43.4	50.5	51.0	53.2	61.5
12	47.8	47.7	53.5	46.2	39.5	52.0	51.5	51.0	45.0
13	51.3	48.8	56.5	52.3	43.8	43.5	41.3	42.5	65.5
14	45.3	43.2	38.0	39.8	40.5	43.5	—	—	—
15	40.2	39.5	43.0	—	—	—	40.3	40.5	41.5
16	50.0	47.2	44.0	—	—	—	48.5	43.8	43.0
17	65.0	67.2	56.5	—	—	—	—	—	—
18	43.3	46.8	33.5	—	—	—	—	—	—
	n = 18	n = 18	n = 14	n = 14	n = 14	n = 10	n = 11	n = 11	n = 9
Mean	49.7	48.5	47.8	43.9	40.5	46.1	48.3	47.1	49.5
±SD	±5.9	±5.9	±8.5	±3.9	±4.1	±4.4	±5.2	±5.3	±8.7
Control subjects									
1	52.3	58.3	51.0	43.8	40.8	39.0	—	—	—
2	51.5	48.0	58.0	46.7	45.5	59.5	—	—	—
3	53.0	56.0	52.0	40.7	41.7	41.0	—	—	—
4	47.7	46.3	45.5	45.0	41.7	45.5	—	—	—
5	45.2	40.3	39.0	47.5	46.3	40.0	—	—	—
6	50.3	50.2	47.0	—	—	—	—	—	—
	n = 6	n = 6	n = 6	n = 5	n = 5	n = 5			
Mean	50.0	49.9	48.8	44.7	43.2	45.0			
±SD	±3.0	±6.6	±6.5	±2.7	±2.5	±8.5			

*Basal ganglia region **Patients 1–6 are predominantly unilaterally and 7–18 bilaterally affected (*see text*) cerebellum showed a heterogeneous response, ranging from −20.5 to +29.7% (mean −3.3%, $P = 0.48$).

The rCMRO$_2$ decreased slightly after L-DOPA administration in all regions. The mean difference in the cortical region was −3.8% (range +3.3 to −13.6%). In the basal ganglia region the response was more heterogeneous with a mean difference of −2.1% (range −28.5 to +20.3%). The cerebellum showed a mean difference of −7.7% (range −20.7 to +13.8%).

Since rCBF clearly increased and rCMRO$_2$ fell only slightly, the rOER decreased significantly in the cortex (with the exception of Cases 5 and 13) and in the basal ganglia (in all patients), but not in the cerebellum. The difference in the cortical region ranged from +2.3 to −27.0% (mean −11.1%, $P < 0.0001$) and in the basal ganglia region from +2.3 to −30.9% (mean −15.4%, $P < 0.0001$). The cerebellum again showed a more heterogeneous response with a range of +20.2 to −35.6% (mean −4.1%, $P = 0.35$).

The acute effects of L-DOPA on rCBF, rCMRO$_2$ and rOER are illustrated in fig. 4, the physiological tomographic images from a typical case (Case 7).

TABLE 6 REGIONAL CEREBRAL METABOLIC RATE OF OXYGEN (rCMRO$_2$)

				Scans after L-DOPA					
	Baseline scan			*After 1 h*			*After weeks*		
Patient No **	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*	*Cortex*	*BG**	*Cerebellum*
1	3.83	3.77	5.05	3.43	3.97	4.25	3.47	3.85	3.90
2	3.87	3.82	4.10	3.77	3.78	3.25	—	—	—
3	3.18	3.25	—	3.17	3.20	—	3.30	3.35	—
4	3.45	4.02	—	3.45	3.77	—	—	—	—
5	3.15	3.43	—	2.77	2.82	—	3.05	3.32	—
6	3.90	3.78	5.30	3.50	3.73	5.30	—	—	—
7	4.55	3.65	4.60	4.70	4.28	3.75	3.77	3.50	3.15
8	3.62	3.48	—	3.30	3.18	—	—	—	—
9	3.97	3.96	4.70	3.97	2.83	4.05	3.67	3.05	4.70
10	3.32	2.83	3.25	2.87	2.93	3.35	3.58	3.48	3.40
11	3.93	3.92	3.35	3.83	3.88	3.30	4.15	4.23	2.70
12	3.11	2.67	2.90	3.15	2.42	3.30	3.45	3.67	3.35
13	3.02	2.22	4.00	3.03	2.67	3.35	2.93	2.40	4.95
14	3.05	2.75	3.60	3.12	2.72	3.35	—	—	—
15	4.13	4.13	3.40	—	—	—	3.53	3.35	3.40
16	3.12	3.62	3.70	—	—	—	3.55	3.70	2.80
17	3.50	3.80	2.80	—	—	—	—	—	—
18	3.42	3.33	3.65	—	—	—	—	—	—
	n = 18	n = 18	n = 14	n = 14	n = 14	n = 10	n = 11	n = 11	n = 9
Mean	3.57	3.47	3.89	3.43	3.30	3.73	3.50	3.45	3.59
±SD	±0.44	±0.53	±0.78	±0.51	±0.59	±0.66	±0.33	±0.47	±0.78
Control subjects									
1	4.05	3.55	3.95	3.82	4.22	4.55	—	—	—
2	2.80	2.43	4.90	4.00	3.08	3.55	—	—	—
3	4.37	3.93	4.80	3.47	3.33	3.80	—	—	—
4	4.03	3.93	4.30	4.08	3.88	3.50	—	—	—
5	3.38	3.30	3.45	3.18	3.10	3.35	—	—	—
6	4.18	4.52	3.50	—	—	—	—	—	—
	n = 6	n = 6	n = 6	n = 5	n = 5	n = 5			
Mean	3.80	3.61	4.15	3.71	3.52	3.75			
±SD	±0.59	±0.71	±0.63	±0.38	±0.51	±0.48			

*Basal ganglia region **Patients 1–6 are predominantly unilaterally and 7–18 bilaterally affected (*see text*)

Control subjects. The response to L-DOPA in this group was very similar to that of the patients (Tables 4–7, fig. 3). However, statistical significance was not reached because of the small number of control subjects. The rCBF increased on average by +17.0% (range −5.5 to +60.8%) in the cortex and +17.6% (range −14.5 to +59.4%) in the basal ganglia. The cerebellum showed an average decrease of −10.9% (range +15.2 to −27.6%). The rOER in this group also showed a marked decrease in response to the rise of rCBF and a slight fall in rCMRO$_2$. The mean change of rOER in the cortical region was −9.9% (range +5.2 to −23.2%) and in the basal ganglia −11.2% (range +14.9 to −30.0%). The cerebellum showed a mean difference of −7.9% (range +2.6 to −23.5%).

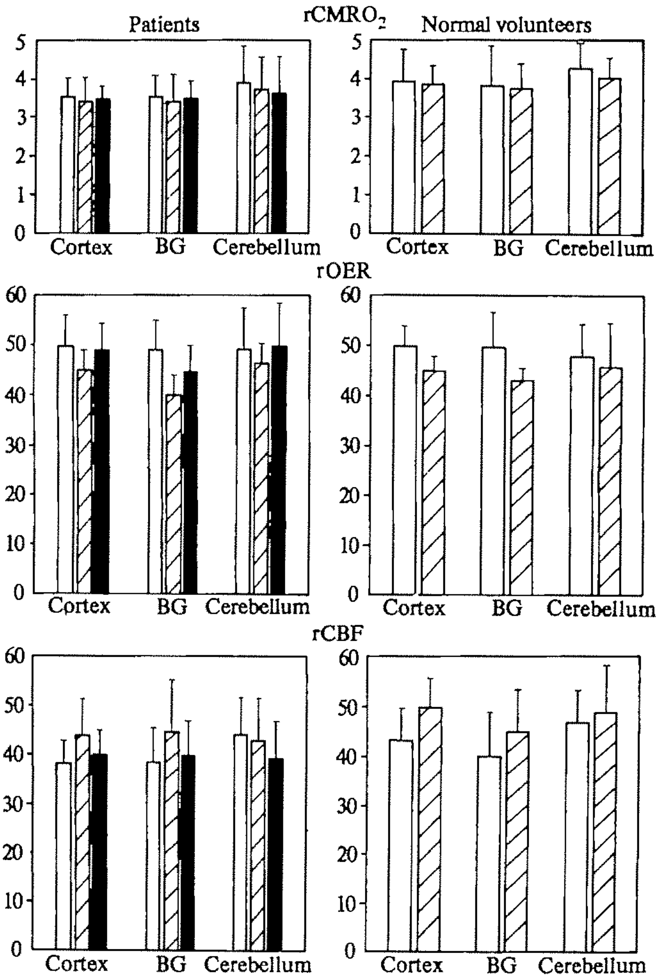

FIG. 3. The effects of L-DOPA on rCMRO$_2$ rOER and rCBF The histograms are the means ±SD for the rCBF, rOER and rCMRO$_2$ of the patient groups and the normal volunteers, (A) before (open areas), (B) after acute oral administration of L-DOPA (hatched areas) and (C) after several weeks' optimal treatment with L-DOPA (shaded area). BG = basal ganglia.

TABLE 7. MEAN PERCENTAGE DIFFERENCE AFTER ACUTE ORAL ADMINISTRATION OF L-DOPA

		rCBF	*rOER*	*rCMRO$_2$*
Patients (n = 14)	Cortex	↑ 13.0*	↓ 11.1**	↓ 3.8
	BG	↑ 20.1*	↓ 15.4**	↓ 2.1
	Cerebellum	↓ 3.3	↓ 4.1	↓ 7.7
Control subjects (n = 5)	Cortex	↑ 17.0	↓ 9.9	↓ 2.4
	BG	↑ 17.6	↓ 11.2	↓ 4.6
	Cerebellum	↑ 0.9	↓ 7.9	↓ 10.9

$^*P < 0.005$. $^{**}P < 0.0001$.

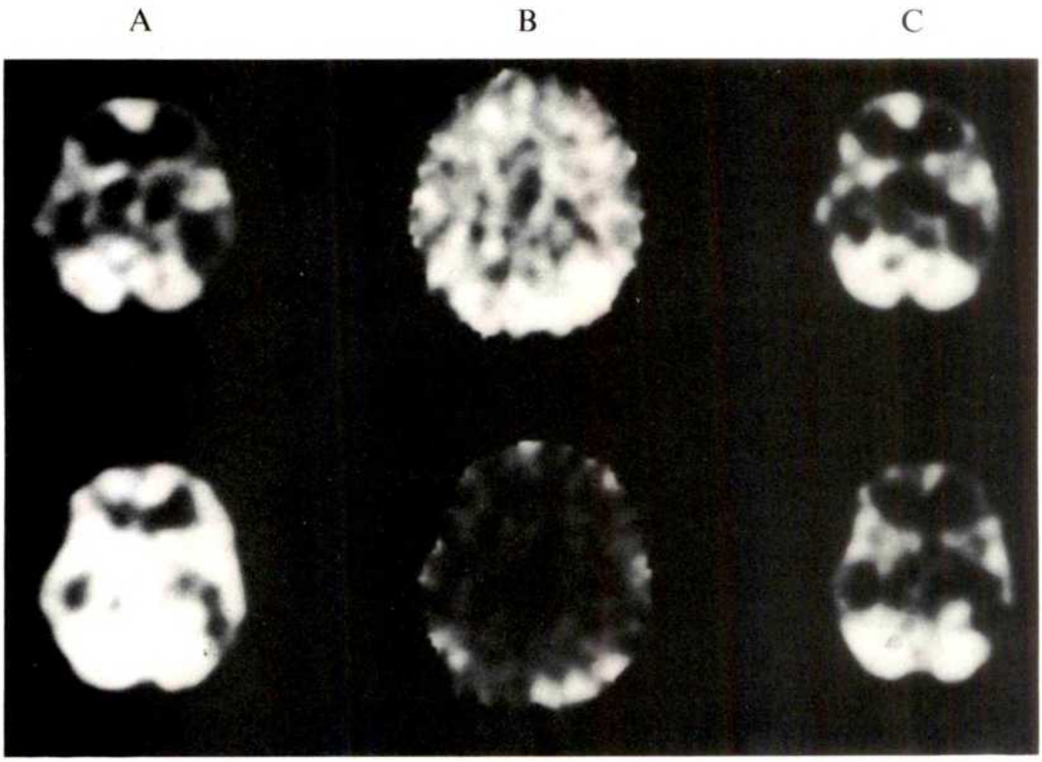

Fig. 4. The tomographic images are shown of a patient with Parkinson's disease depicting (A) rCBF, (B) rOER and (C) rCMO$_2$ before (*top row*) and after (*bottom row*) acute oral treatment with L-DOPA and carbidopa. All images are taken at the same level (4.5 cm above the orbitomeatal line) cutting through the basal ganglia. The left side of the brain is always on the left side of the image and the frontal lobe of the brain is at the top of the image. The images before and after treatment have an identical scale. After treatment a diffuse rise of the cerebral blood flow is seen with almost no change of oxygen utilization. As a result the fractional oxygen extraction decreases.

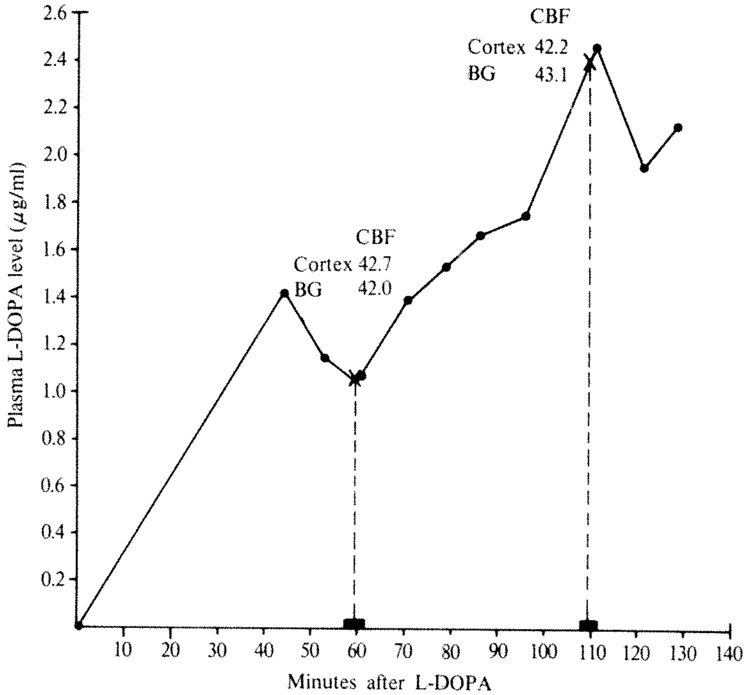

FIG. 5. The plasma L-DOPA level (μg/ml) in a patient over time (min) after oral administration of L-DOPA and carbidopa. The cerebral blood flow (CBF), measured on two separate occasions, remained almost unchanged in spite of a considerable increase in plasma L-DOPA level.

Relationship between the Changes of rCBF and Other Variables

The small changes in pCO_2 after L-DOPA did not correlate with the changes in rCBF ($r = 0.46$, $P < 0.10$). The observed differences in rCBF did not correlate with the dose of L-DOPA in mg/kg given to each subject, nor with the improvement of clinical disability or the disease duration amongst the patient group. There was some correlation between the percentange change of rCBF in the cortex and the plasma L-DOPA level ($r = 0.63$, $P < 0.01$), but this was not the case with the change of rCBF in the basal ganglia regions ($r = 0.37$, n.s.).

In 4 subjects serial rCBF scans and arterial samples were taken to establish a curve of the plasma L-DOPA level and the corresponding brain blood flow response. Two examples are shown in figs 5 and 6. In the first subject the plasma L-DOPA level increased substantially between 60 and 110 min, while rCBF remained virtually unchanged. The second subject showed a slight increase in rCBF at a time when the plasma L-DOPA level had started to fall. The 2 other subjects showed a similar absence of any direct relationship between the rCBF changes and the changes in plasma L-DOPA level over time.

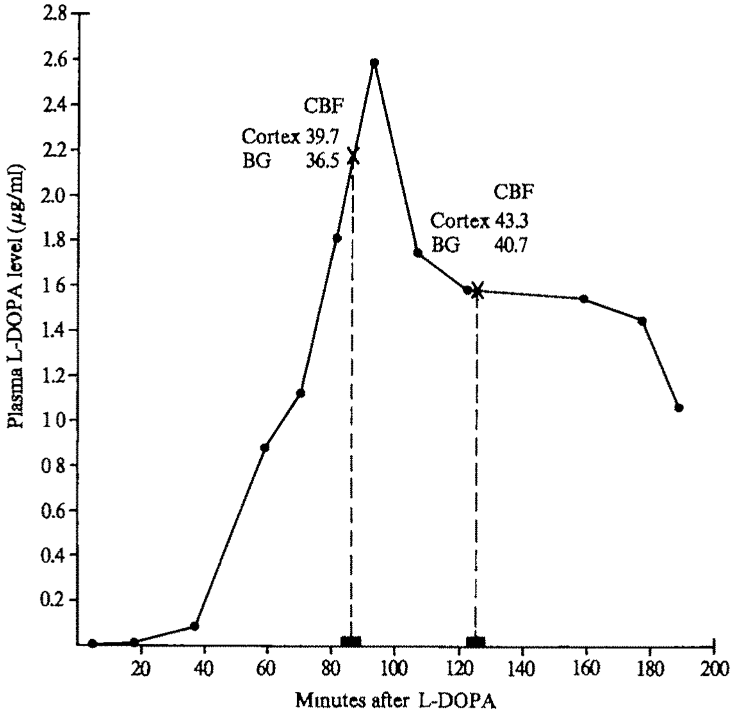

FIG 6. The course of the plasma L-DOPA level after oral administration of L-DOPA and carbidopa in a normal volunteer. The CBF, measured on two occasions, showed an increase whereas the plasma L-DOPA level was already decreasing.

Follow-up Measurements on Maintenance L-DOPA Therapy

In the patients scanned after several weeks of L-DOPA treatment, values in cortex and basal ganglia regions had returned almost to their baseline levels. There had been a fall of rCBF and a slight rise of rCMRO$_2$ since the scan immediately after acute L-DOPA administration (Tables 5–7, fig. 3). Despite this evolution of the physiological changes, the degree of clinical improvement was maintained at its original level (fig. 1).

DISCUSSION

Our study shows that acute administration of L-DOPA in clinically effective doses has a marked influence on the cerebral blood flow. The drug increased mean rCBF by 13 per cent in the cerebral cortex and by 20 per cent in the basal ganglia region in the patient group. These differences are highly significant. The control population showed the same pattern and degree of response although the changes did not reach statistical significance because of the small number of subjects.

In contrast, no consistent change of rCBF was observed in the cerebellum. The average change was very small, although the individiual response was quite heterogeneous.

Cerebral oxygen utilization tended to decrease in all regions after L-DOPA administration although the differences were usually very small, ranging from 2 to 5 per cent in the cortex and basal ganglia. The cerebellum showed a greater decrease in oxygen utilization, which was most marked in the control population (mean 10.9%).

As a consequence of the increase in cerebral blood flow and slight fall of oxygen utilization there was a considerable reduction of fractional oxygen extraction (rOER) in the affected regions of the brain.

It was notable that the increase in rCBF was not paralleled by a rise in $rCMRO_2$. In view of the decreased rOER and almost unchanged $rCMRO_2$, we consider the diffuse increase in rCBF after administration of L-DOPA to be a consequence of direct vasodilatation by the drug and not a response to local metabolic demands. This is supported by our findings from the scans performed several weeks after optimal treatment with L-DOPA and carbidopa. At that stage the rCBF had decreased again without any appreciable change of $rCMRO_2$ (resulting in a rise of rOER towards its baseline value), while the degree of clinical improvement remained as good as it had been after the acute administration of L-DOPA. We have excluded the possibility of an independent effect of carbidopa on cerebral blood flow by giving this drug separately before the baseline scan.

The characteristic regional differences in the baseline scans of the predominantly unilateral patients compared to bilateral patients and normal controls will be reported separately. No difference in response to L-DOPA treatment was found between the asymmetric and bilateral group of patients. The disappearance of tremor during the second scan one hour after L-DOPA administration was not accompanied by a specific change of oxygen utilization either locally or globally. Instead the diffuse increase in CBF was of the same magnitude in both groups of patients.

Stimulation of the dopaminergic system tends to increase cerebral blood flow both in animals and in man, either on a global or regional level (von Essen, 1974; von Essen and Roos, 1974; Toda, 1976; McCulloch and Harper, 1977; Edvinsson *et al.*, 1978; McCulloch and Edvinsson, 1980; Güell *et al.*, 1982; Jauzac *et al.*, 1982; McCulloch, Kelly and Ford, 1982; Bès *et al.*, 1983; McCulloch, 1983). Most of these studies have been performed with the dopaminergic agonists apomorphine or piribedil, some with dopamine. In general, administration of dopaminergic agonists experimentally in animals results in a marked increase of cerebral blood flow. Melamed *et al.* (1978) studied 26 patients with Parkinson's disease using xenon-133 inhalation technique before and after chronic administration of levodopa and a peripheral dopa-decarboxylase inhibitor. These authors did not find a significant alteration in hemisphere or regional blood flow in response to levodopa. However, no acute studies were performed and their finding is in agreement with our results of the PET scan performed several weeks after regular optimal L-DOPA therapy. Ekström-Jodal *et al.* (1974) measured in anaesthetized dogs the effect of L-DOPA on hemisphere blood flow using a radioactive gas elimination technique with external γ-registration. They found signs of an increase of the cerebral blood flow after L-DOPA followed later by a decrease. No changes in global arteriovenous oxygen differences were found after administration of L-DOPA. Dose-dependent vasodilatation has been observed following direct application of dopaminergic agonists on actively contracting pial arteries both *in vitro* and *in vivo* (Edvinsson *et al.*, 1978).

With regard to the effects of L-DOPA on cerebral metabolism, the results of animal studies by other groups differ from our observations in man. McCulloch and Harper (1979) showed in anaesthetized baboons that administration of apomorphine, a dopaminergic receptor agonist, produces global increase in cerebral blood flow, oxygen consumption and glucose uptake. The increase in cerebral blood flow, however, was far in excess of the increase in cerebral metabolism. This may have been due to the fact that the animals were anaesthetized. As Grome and McCulloch (1983) have shown, use of the anaesthetic chloral hydrate depresses local cerebral glucose utilization and modifies the local metabolic response to apomorphine.

Also in anaesthetized baboons, McCulloch and Edvinsson (1980) found a global increase of cerebral blood flow and oxygen metabolism after administration of the putative dopaminergic agonist piribedil. Pimozide, a putative dopaminergic antagonist, prevented these effects. McCulloch, Kelly and Ford (1982) showed that administration of apomorphine in conscious rats produces a coupled increase in rCBF and local glucose utilization in certain cortical and subcortical brain regions. They concluded that the rise of cerebral blood flow, at least in their study, was a secondary response to the increase in local tissue metabolic activity.

In support of our findings, Rougemont *et al.* (1983) did not observe any increase in regional glucose utilization (measured by PET and the ^{18}F-deoxyglucose technique), in 4 patients with Parkinson's disease studied before and after drug therapy. Their study, however, had some methodological shortcomings: only 4 patients were investigated, after a very short withdrawal of their medication and the therapeutic regimen was a mixture of antiparkinsonian drugs.

The reason for our inability to demonstrate an increase in oxygen utilization, particularly in the basal ganglia region, is not immediately clear. This disparity with the results of animal studies may be partly explained by methodological factors. With the relatively low spatial resolution of the ECAT II tomographic camera, subtle changes of flow or metabolism confined to small regions of brain could be overlooked. Large global increases of oxygen metabolism of the sort observed in some animal studies would not have gone undetected, even in the relatively small basal ganglia regions. Another point is that we used L-DOPA, and not a dopaminergic agonist such as apomorphine or piribedil. The pharmacological effects of L-DOPA on the cerebral vessels may have overshadowed more subtle local influences on brain regions such as the basal ganglia. On the other hand, in view of the marked clinical response in our patients (*see* fig. 1), it seems reasonable to assume that sufficient L-DOPA had penetrated the basal ganglia to cause a clear change in tissue metabolism, if such a change is indeed a consequence of adequate dopaminergic stimulation. It has been shown in animal studies that the concentration of plasma levodopa correlates closely with the concentration of dopamine in the striatum (Doller and Connor, 1980). However, we found no correlation between the plasma L-DOPA level and the degree of clinical improvement. This may be because striatal dopamine replenishment is not synchronous with clinical improvement, as suggested by Rossor *et al.* (1980), who discussed the difficulties in relating plasma L-DOPA and dopamine levels to clinical response. In our study, the peak plasma L-DOPA level showed moderate correlation with the magnitude of the rise of rCBF in the cortex ($r = 0.63$, $P < 0.01$) but not in the basal ganglia region. This suggests that apart from a direct action on blood vessels there may be an additional metabolic factor contributing to the rise in rCBF, particularly since the absolute increase in rCBF was greater in the basal ganglia region than in the cortex in the patient group. Ingvar *et al.* (1983) found that systemic administration of the dopamine receptor agonist apomorphine leads to a general increase of CBF in the normal rat. The magnitude of the circulatory change induced by apomorphine varied considerably between different regions but seemed not directly related to the distribution and density of dopamine terminal axons or dopamine receptors. This group found in some regions a change in blood flow coupled to a change in glucose metabolism (e.g. in the nucleus accumbens) but, in several other regions (e.g. in some neocortical areas), there was a marked increase in CBF and no change in local metabolic rate. We failed to show a direct relation between the plasma L-DOPA level and rCBF over time in 4 individuals (*see* figs. 5 and 6), indicating the complexity of the situation regarding factors that regulate rCBF.

Although the $paCO_2$ change in our study may have contributed to a small extent to the increase in rCBF (which ranged from 13 to 20%), this seems unlikely because the $paCO_2$ changes were small and in the physiological range. Also, there was no correlation between the change of $paCO_2$ in each subject and the increase in rCBF in either cortex or basal ganglia.

Whether the small decrease of $rCMRO_2$ (2.0–4.6% in cortex and basal ganglia) after the acute administration of L-DOPA was due to chance or a consequence of a methodological bias is also difficult to assess. In favour of the first option is the fact that after a few weeks of optimal treatment with L-DOPA the $rCMRO_2$ had returned to the baseline values.

The different response in the cerebellum was conspicuous, but not surprising in view of the much lower density of dopaminergic receptors in the cerebellum in comparison with the rest of the brain (Laduron and Leysen, 1977). To our knowledge, no study has been published investigating the presence of dopaminergic receptors in isolated cerebellar blood vessels.

ACKNOWLEDGEMENTS

We would like to thank Mr D. D. Vonberg and the staff of the MRC Cyclotron Unit, Hammersmith Hospital, for making this study possible. Especially we are grateful to Mr P. Buckingham for dispensing gases, Ms M. Almeida for technical assistance and Ms R. Jackson for assistance in the preparation of the manuscript. In addition we would like to thank Merck, Sharp and Dohme for kindly providing us with carbidopa.

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(*Received March 29, 1984. Revised August 20, 1984. Accepted August 31, 1984*)

Brain (1985), **108**, 193–224

THE SPECTRUM OF CORTICAL MYOCLONUS

FROM FOCAL REFLEX JERKS TO SPONTANEOUS MOTOR EPILEPSY

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SUMMARY

The purpose of this paper is to draw attention to the wide range of clinical motor phenomena which may be caused by abnormal sensorimotor cortical discharge. Eleven selected patients with cortical myoclonus are described. In all cases the brief muscle jerks appeared to involve cerebral cortical mechanisms, for there were enlarged cerebral evoked potentials to somatosensory or visual stimuli and (in 5 of the 6 cases investigated in this way) a time-locked cortical event preceded spontaneous or action-induced jerking. In some patients, cortical myoclonus occurred only in response to a variety of afferent inputs (cortical reflex myoclonus). In others, the myoclonus occurred only during movement, when cortical mechanisms were activated voluntarily (cortical action myoclonus), or the cortical discharge occurred spontaneously (spontaneous cortical myoclonus and epilepsia partialis continua), and even spread to cause focal motor epilepsy (Jacksonian seizures). Some patients showed combinations of stimulus sensitive and spontaneous myoclonus, epilepsia partialis continua, focal motor epilepsy and generalized grand mal seizures. Such variations probably represent subtle differences in the site of abnormality in sensorimotor cortical neuronal mechanisms.

INTRODUCTION

Brief muscle jerks that do not have the random flow of chorea or the stereotypy and temporary willed inhibition of tics are called myoclonus. Although muscle twitches may be produced by disease of the peripheral nervous system, for example the fasciculations of motor neuron disease, the term myoclonus is employed to describe muscle jerks arising in the central nervous system. Myoclonus may be produced by abnormal discharge in many parts of the spinal cord and brain. *Segmental myoclonus*, restricted to one part of the body, is caused by spontaneous discharge, often repetitive, in spinal cord or brainstem. Another form of myoclonus, *reticular myoclonus*, is produced by discharges commencing in the brainstem. The commonest type of myoclonus arises in the cerebral cotex, *cortical myoclonus*.

The earliest evidence for the participation of the motor cortex in the generation of myoclonus was provided by Dawson (1947), who studied a patient with focal generalized jerks provoked either by muscle stretch produced by tapping a limb with a tendon hammer, or by electrical stimulation of a peripheral nerve. The electrical stimuli not only caused muscle jerking, but also produced giant somatosensory evoked potentials. Dawson concluded that 'these responses to stimulation are cerebral in origin'. Further evidence for the existence of muscle jerking arising in the motor cortex was provided by Kugelberg and Widén (1954) who described a patient with spontaneous, repetitive jerky contractions of the right foot, preceded by focal EEG spikes recorded at electrocorticography from the medial surface of the opposite motor cortex. Subsequent surgical excision of this small zone abolished the myoclonus of the foot. Pagni *et al.* (1971) briefly reported a patient with stimulus-sensitive myoclonus who was studied by electrodes implanted into the thalamus, sensory cortex, motor cortex, and internal capsule. They concluded that the jerks were caused by discharge of afferent impulses in the spinal dorsal columns, a subsequent sensorimotor cortex discharge, and then the efferent volley passing down the corticomotoneuron pathway.

Halliday (1967), in an influential review on myoclonus, distinguished 'pyramidal' myoclonus with origin in motor cortex, from myoclonus arising in other sites—'both experimental and clinical findings suggest that there is a type of myoclonic jerking, characterised by a brief, hypersynchronous discharge in the electromyogram, which closely follows a spike discharge in the contralateral cortex and depends on impulses conducted down the pyramidal tract'. He drew attention to the frequent description of patients with spontaneous myoclonus associated with focal spike discharges arising from the opposite sensorimotor cortical area. In addition, he mentioned the patient described by Dawson as an example of the uncommon situation in which peripheral stimuli could evoke myoclonic jerking. Subsequently, Sutton and Mayer (1974), and Rosén *et al.* (1977) each described individual patients with similar stimulus-sensitive myoclonus of cortical origin. Hallett *et al.* (1979) added a detailed electrophysiological description of such stimulus-sensitive myoclonus in 3 further cases and introduced the term cortical reflex myoclonus to describe the syndrome. Meanwhile, Shibasaki and Kuroiwa (1975) established that spontaneous myoclonus might be due to cortical discharge even though the routine surface EEG showed no abnormality. They employed the technique of back-averaging the EEG prior to the myoclonus by triggering from the EMG burst responsible for the jerk. By this means, they were able to extract from the averaged EEG a potential arising over the sensorimotor cortex preceding the muscle jerk by a short interval appropriate to conduction in corticomotoneuron pathways. Chadwick *et al.* (1977) independently developed the same technique to show not only the existence of a motor potential in averaged records that was not apparent in simple surface EEG recordings in some cases of cortical myoclonus, but also the lack of correspondence of surface EEG spikes to myoclonic jerks in other patients. Thus in a case of what they described as reticular reflex myoclonus, a large EEG spike, which superficially appeared linked to the myoclonic twitches, disappeared on back-averaging, indicating that it was not time-locked to the muscle discharges (Hallett *et al.*, 1977). The use of this technique of back-averaging went a long way to clarify the mystery of the relationship of the EEG to myoclonic jerks. Many previous observers had found it difficult to interpret the significance of the presence or absence of spike discharges in the EEG, and their time relation to myoclonic twitches. It was not until it was possible to establish whether such EEG spikes were time-locked to the muscle jerks, or whether any other form of EEG abnormality could be averaged in relation to muscle twitches, that the true significance of cortical discharge in relation to myoclonus could be appreciated.

Subsequent experience has increased our understanding of the various types of cortical myoclonus. We have now encountered a series of patients with different combinations of stimulus-sensitive and spontaneous myoclonus, who may or may not have epilepsia partialis continua, focal motor epilepsy, or secondarily generalized grand mal seizures. The purpose of this paper is to draw attention to the range of clinical phenomena which may be caused by abnormal cortical discharge. At one extreme, cortical myoclonus may occur only in response to afferent input. At the other extreme, motor cortex discharge may occur spontaneously and spread to cause focal motor epilepsy. We describe here a group of patients illustrating the spectrum between the extremes. Such variations probably represent subtle differences in the site of abnormality within the neuronal machinery of the sensorimotor cortex.

PATIENTS

From those patients with different types of myoclonus referred to our two departments for investigation and treatment, we have selected 11 cases to illustrate the range of cortical myoclonus. We have not included examples of pure epilepsia partialis continua, where the cortical origin of the repetitive muscle jerking is obvious from simple EEG studies. Epilepsia partialis continua has been the subject of reviews by Juul-Jensen and Denny-Brown (1966), and by Thomas *et al.* (1977) (*see* Discussion for definition).

We define cortical myoclonus as muscle jerking originating from abnormal electrical discharge in the cerebral cortex. The cortical origin of the muscle jerking may be deduced from (1) spike discharges in the routine EEG preceding the muscle EMG bursts responsible for the myoclonus, as in many cases of typical epilepsia partialis continua; (2) the discovery of an EEG potential preceding the EMG bursts responsible for the myoclonus by the technique of back-averaging (*see below*) (Cases 4, 8, 9, 10 and 11); (3) the provocation of myoclonus by external stimuli, which also caused abnormal cerebral evoked potentials recorded from the surface of the scalp over the sensorimotor cortex or elsewhere (Cases 1, 2, 3, 5, 6, 7, 8, 9 and 11).

The general clinical details of these patients are summarized in Table 1, the features of their myoclonus in Table 2, and the results of investigations in Table 3. Despite extensive investigation, a pathological diagnosis could not be established in some of these patients, particularly those with focal cortical abnormalities (Cases 6, 9, 10 and 11). Other patients were diagnosed on clinical grounds as examples of (1) olivopontocerebellar atrophy (Cases 1 and 3) in whom a cerebellar ataxia began in adult life, with additional parkinsonism, and evidence on CT scans of brainstem and cerebellar atrophy; (2) early onset autosomal recessive cerebellar ataxia with retained tendon reflexes (Case 2), where cerebellar ataxia began in childhood, but with preserved tendon reflexes; (3) dyssynergia cerebellaris myoclonica, or the Ramsay Hunt syndrome (Cases 4, 5 and 7) in whom severe action myoclonus was accompanied by cerebellar ataxia, with or without seizures; and (4) posttraumatic myoclonus (Case 8).

TABLE 1. CLINICAL FEATURES OF PATIENTS WITH CORTICAL MYOCLONUS

	Case 1 (*M.R*)	*Case 2* (*J J*)	*Case 3* (*P.R L*)	*Case 4* (*J A*)	*Case 5* (*C.G*)	*Case 6* (*J M*)	*Case 7* (*J D.*)	*Case 8* (*E.A.*)	*Case 9* (*J.B.*)	*Case 10* (*F.M.*)	*Case 11* (*P M.*)
Sex	F	F	F	F	F	M	F	F	F	M	M
Age at onset (yrs)	60	15	55	19	63	67	3	22	30	60	9
Duration of illness (yrs)	5	9	12	8	4	2	12	33	3	weeks	12
Initial symptoms	Gait ataxia, falls	Gait ataxia, falls	Parkinsonism	Falls	Falls	Jerking R hand	Absence seizures	Seizures	Jerking R hand	Seizures	Seizures
Family history	N	+	N	N	N	N	N	N	N	N	N
Seizures	N	N	N	+/−	N	N	+++	+	+	+	+++
Dementia	N	N	N	N	N	++	N	N	N	N	N
Speech	Dysarthric	Dysarthric	Dysarthric	Dysarthric	N	Dyphasia	N	Dysarthric	N	N	N
Gait	Ataxic +++	Ataxic +++	Parkinsonian +++	Ataxic +++	Ataxic +++	N	Ataxic ++	Ataxic ++	N	N	N
Optic fundi	N	N	N	N	N	N	N	N	N	N	N
Eye movements	N	Nystagmus	Dysmetria	Dysmetria	N	N	N	N	N	Nystagmus	N
Other cranial nerves	N	N	Dysphagia	N	N	N	N	N	N	N	N
Limb ataxia	++	++	N	?	++	RUL	++	?	N	?	RUL
Muscle power	N	N	Akinetic rigid	N	N	N	N	N	N	?	N
Tendon reflexes	N	++	++	N	N	N	N	N	N	N	N
Plantar responses	N	E/F	E/F	N	N	N	N	N	N	N	N
Sensation	N	N	N	N	N	N	N	N	N	N	Abn
Other	Parkinsonism		Parkinsonism				Scoliosis, pes cavus				
Clinical diagnosis	OPCA (sporadic)	EOCA (autosomal recessive)	OPCA (sporadic)	DCM	DCM	?	DCM	Posttraumatic myoclonus	?	?	?

? = patients with action myoclonus in whom it was difficult to decide whether additional ataxia was present. Ataxia and seizures are graded as mild (+), moderate (++) or severe (+++). Plantar responses: E = extensor; F = flexor; E/F = one extensor OPCA = olivopontocerebellar atrophy EOCA = early onset cerebellar ataxia with retained tendon reflexes DCM = dyssynergia cerebellaris myoclonica N = normal or not present. RUL = right upper limb

TABLE 2 CLINICAL FEATURES OF MYOCLONUS

	Case										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Distribution of myoclonus*											
Focal	0	0	0	0	0	+	0	0	+	+	+
Multifocal	+	+	+	+	+	0	+	+	0	0	0
Generalized	0	0	+	0	0	0	0	+	0	0	0
Type of myoclonus											
Spontaneous	0	0	0	0	0	0	0	+	+	+	+
Action	0	0	0	+	+	+	+	+	+	+	+
Reflex	+	+	+	0	+	+	+	+	+	0	+
Epilepsia partialis continua	0	0	0	0	0	0	0	0	+	+	+
Provoking stimuli											
Pin-prick	+	0	+	0	0	+	0	0	+	0	+
Touch	+	0	+	0	0	+	0	0	+	0	+
Muscle stretch	0	+	+	0	0	+	0	+	+	0	+
Noise	0	0	0	0	0	0	0	0	0	0	0
Visual	0	0	+	0	0	0	+	0	0	0	0
Electrical digital nerve stimulation	+	0	+	0	+	+	+	+	+	0	+

* Focal = muscle jerks occurring in one limb. Multifocal = muscle jerks occurring in more than one body part, if spontaneous, the jerks occur independently in different parts of the body, if induced by movement or external stimuli, the jerks occur in the part moved or stimulated. Generalized = muscle jerks occurring approximately synchronously in many body parts, either spontaneously, or on movement or stimulation; moving or stimulating one part of the body causes synchronous jerking of other parts of the body.

TABLE 3 INVESTIGATIONS IN PATIENTS WITH CORTICAL MYOCLONUS

	Case										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Chest x-ray	N	N	N	N	N	N	N	N	N	N	N
CT Scan*	CbA BsA	CbA	CbA BsA	N	N	CoA	CbA	N	N	N	N
Routine EEG	N	N	N	N	N	Abn	Abn	Abn	Abn	Abn	Abn
VER (pattern stimuli)	N	N	N	N	N	N	N	N	N	—	N
Nerve conduction studies	N	N	N	N	N	N	N	N	—	—	N
CSF examination	N	—	N	N	N	N	N	N	N	Abn	N
Serology	N	N	N	N	N	N	N	N	N	N	N
Copper and caeruloplasmia	—	N	—	N	N	N	N	—	—	—	—
Calcium	N	N	N	N	N	N	N	N	N	N	N
Thyroid function	N	N	N	N	N	N	N	N	N	N	—
Hexosaminidase	—	N	—	N	N	—	N	—	—	—	—
β-galactosidase	—	N	—	N	N	—	N	—	—	—	—
Arylsulphatase A	—	N	—	N	N	—	N	—	—	—	—
Muscle biopsy	—	—	—	N	N	—	—	—	—	—	—
Mitochondrial enzymes	—	—	—	N	—	—	—	—	—	—	—
Rectal biopsy	—	—	—	N	—	—	—	—	—	—	—
Skin biopsy	—	—	—	—	N	—	N	—	—	—	—

N = normal, Abn = abnormal. * CoA = cortical atrophy, CbA = cerebellar atrophy; BsA = brainstem atrophy.

METHODS

The methods used have been described in detail before (Rothwell *et al.*, 1984). Only a brief summary will be given here. Patients 4, 6, 8, 9, 10 and 11 were investigated in full in London, using back-averaging techniques and graded muscle stretch stimuli. The other patients were investigated in Spain, using a Medelec MS6 machine to record routine evoked potentials and to investigate the time relationships between somatosensory or visual stimuli and myoclonic muscle jerks.

Preliminary EMG recordings were made from up to eight muscles involved in the jerks using bipolar silver/silver chloride surface electrodes or bipolar needle electrodes (*see* figure legends for individual details). The EEG was recorded monopolarly with surface electrodes fixed to the scalp and referred to a linked mastoid reference. Electrode placements in the text are described with reference to the somatosensory hand area. This was taken to be 7 cm lateral on a line joining the external auditory meatus with a point 2 cm posterior to the vertex. Somatosensory potentials (SEPs) were evoked with a variety of different stimuli including ring electrode electrical stimulation of digital nerves at twice sensory threshold, muscle stretch using low inertia torque motors, and natural cutaneous touch stimuli. In normal volunteers we have never recorded medium latency (< 50 ms) SEPs larger than 12 μV to any of these stimuli when given to the arm, or 2 μV when given to the leg. Back-averaging EEG events preceding spontaneous or action-induced muscle jerks was performed using a computer program devised by Mr H. B. Morton of the National Hospital. One of the muscles most regularly involved in the jerks was used to trigger the computer, which collected and averaged events which occurred before and after the trigger point. Each single sweep was recorded separately and averaged later so that records showing movement artefact or poor triggering could be rejected by eye.

The EEG was recorded using high and low pass filters set at 0.16 and 2.5 kHz, respectively; EMGs were recorded with filters at 80 and 2.5 kHz. SEPs and back-averaged potentials were recorded with a sampling rate of 1 kHz per channel; 32 to 192 responses were averaged in each trial. Labelling of the SEP components is difficult in patients with grossly abnormal potentials. In this paper we have chosen to designate the major peaks by their polarity and sequence (N1, P1, N2, etc.) to avoid equating any of the myoclonic potentials with those seen in normal individuals.

RESULTS

Cutaneous Reflex Myoclonus

Case 1. M.R. (Clinica Universitaria No. 136647), a 65-year-old lady with a five-year history of unexplained falls and unsteadiness of gait. On examination in 1979 she had marked truncal ataxia and limb dysmetria. Walking was still possible, but unsteady, with a wide-based gait. No abnormality was detected on examination of the cranial nerves. Muscle power was normal, and there was no sensory abnormality. All tendon jerks were brisk but symmetrical, and the plantar responses were flexor. No symptomatic cause was found for this cerebellar syndrome and there was no past or family history of neurological disease. Over the next two years the patient became incontinent of urine, could not swallow solid food and became markedly akinetic. She lost facial expression, could not perform fine manual motor tasks at normal speed and lost postural reflexes. At this time she presented a typical parkinsonian syndrome. There was no dementia or cognitive deficit. A CT scan revealed marked atrophy of the cerebellar vermis and brainstem, but the cerebral hemispheres were normal. The patient was diagnosed as a sporadic case of olivopontocerebellar atrophy.

At about this time it was noted that brief light touch or pin-prick of the plantar skin area innervated by the medial plantar nerve of either foot provoked sudden dorsiflexion of the big toe, or of the whole foot, accompanied by plantarflexion of the other toes (fig. 1A). Tapping the tendon of triceps surae with a hammer, or tibialis anterior, did not elicit any jerks other than the usual monosynaptic tendon reflex. There was no visible muscle jerking at rest, or when the patient voluntarily moved the foot or toes.

By 1983 her general condition had deteriorated. Similar stimuli applied to the palmar surface of either hand, particularly to the thumb or forefinger then produced indentical short-lasting and repetitive jerks of the finger flexor muscles.

The reflex myoclonic jerks were not sufficiently severe as to deserve specific treatment. Oral therapy with L-DOPA, with carbidopa (1000/100 mg/day) and bromocriptine (40 mg/day), did not improve her parkinsonian syndrome.

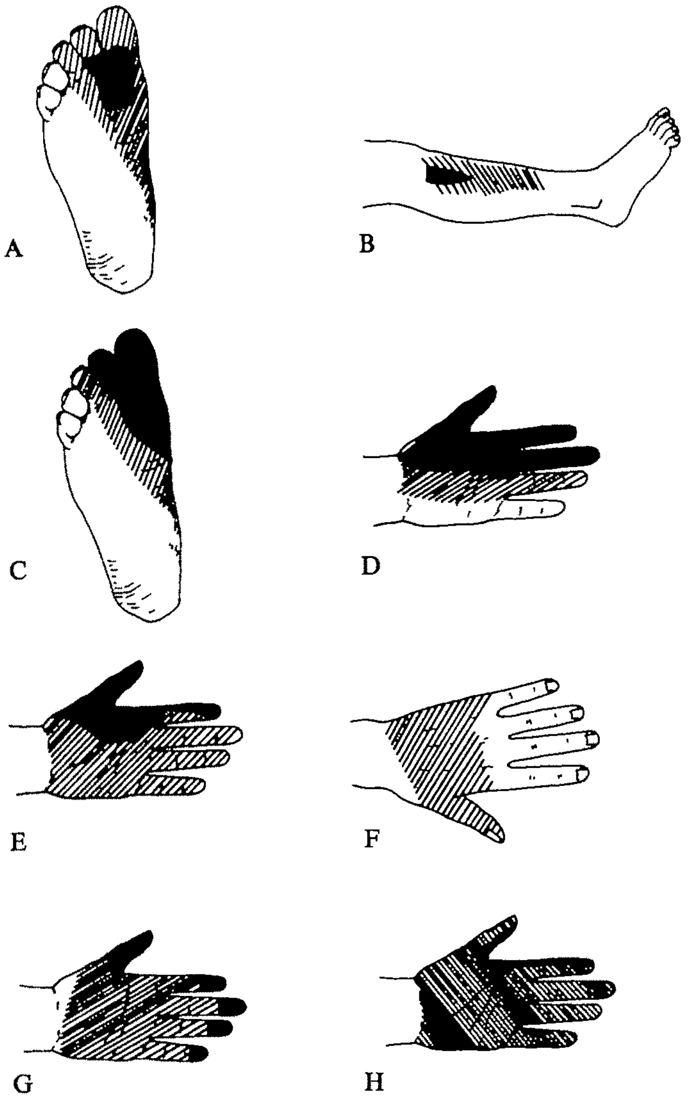


FIG. 1. Approximate extent of cutaneous areas stimulation of which produced myoclonic jerks in Cases 1 (A), 2 (B), 3 (C, D), 6 (E, F), 9 (G) and 11 (H). Dark areas indicate the most sensitive area of the field.

Physiological studies. The latency to the onset of the EMG bursts responsible for the muscle jerk in extensor hallucis longus and tibialis anterior to light touch on the great toe was about 80 ms (fig. 2A). Electrical stimulation of the great toe with ring electrodes elicited a jerk with a similar latency. The duration of the EMG bursts was 25 to 50 ms. A single shock usually caused two or three repetitive bursts which occurred with a period of about 60 ms (fig. 2B).

Vibration at 60 Hz for 30 to 60 s of the plantar surface of the foot or the ankle of the stimulated side abolished the ankle tendon jerks, and reduced the H-wave recorded over the soleus muscle by 50 per cent without affecting the long latency reflex jerks elicited by electrical or tactile stimulation of the toes (fig. 2C).

SEPs could be elicited by a light touch to the toes, sufficient to provoke a jerk, with a latency to the peak of the first positive component of 45 ms. The amplitude of the P1-N2 component recorded 2 cm posterior to the vertex was 5.5 μV, which was ten times larger than control values obtained in normal subjects. Electrical stimulation of the great toe also elicited enlarged SEPs, which were followed by reflex muscle jerks.

Electrical stimulation of the digital nerves of the thumb produced similar jerks in the forearm flexor muscles with a latency to the onset of the EMG bursts of about 40 ms (fig. 2D). Digital nerve stimulation also caused enlarged SEPs recorded from over the somatosensory hand area. The latency to the peak of the first positive component was 22 ms, and the P1-N2 was 25 μV in amplitude (fig. 2D).

Stretch-sensitive Reflex Myoclonus

Case 2. J.J. (Clinica Universitaria No. 126627), a 24-year-old female with a progressive history of postural instability and difficulty in walking since the age of 15 years. Her parents were first cousins. One older brother aged 27 years, and a 20-year-old sister, had a similar disease. There was a marked truncal ataxia, sufficient to make independent standing impossible, and ataxia of the legs on heel-shin testing. There was nystagmus both on vertical and horizontal gaze, and a mild upper limb dysmetria. Otherwise examination of the cranial nerves was normal. Muscle power was normal and there was no sensory defect. The tendon jerks were very brisk and the left plantar response was extensor. The only abnormality observed in a CT scan was atrophy of the cerebellar vermis. The patient was diagnosed as early onset recessively inherited cerebellar ataxia with retained tendon reflexes.

Tendon taps to the anterolateral region of the calf evoked a brief reflex flexion of the toes (fig. 1B). Light touch or pin-prick to the same area or tendon taps to the calf muscles, or to the intrinsic muscles of the foot, did not provoke any jerk. Vibration of the Achilles tendon (60 Hz for 30–45 s) abolished the ankle jerk without influencing the reflex flexion of the toe elicited by tapping the triggering area. Repetitive tapping produced a prolonged contraction of the toe flexors due to summation of the reflex response to each individual tap. Such jerks were not apparent at rest, nor were they evoked by voluntary movement of the foot or toes. The reflex myoclonus was not sufficiently severe to merit any specific drug therapy.

Physiological studies. An electrical shock of a sufficient strength to elicit a small direct muscle twitch, given *via* needle electrodes inserted into the belly of the tibialis anterior, evoked a reflex flexion of the toes. This response was identical to that observed after tapping the same muscle. The reflex EMG discharge, which frequently consisted of two bursts, could be recorded synchronously from the short

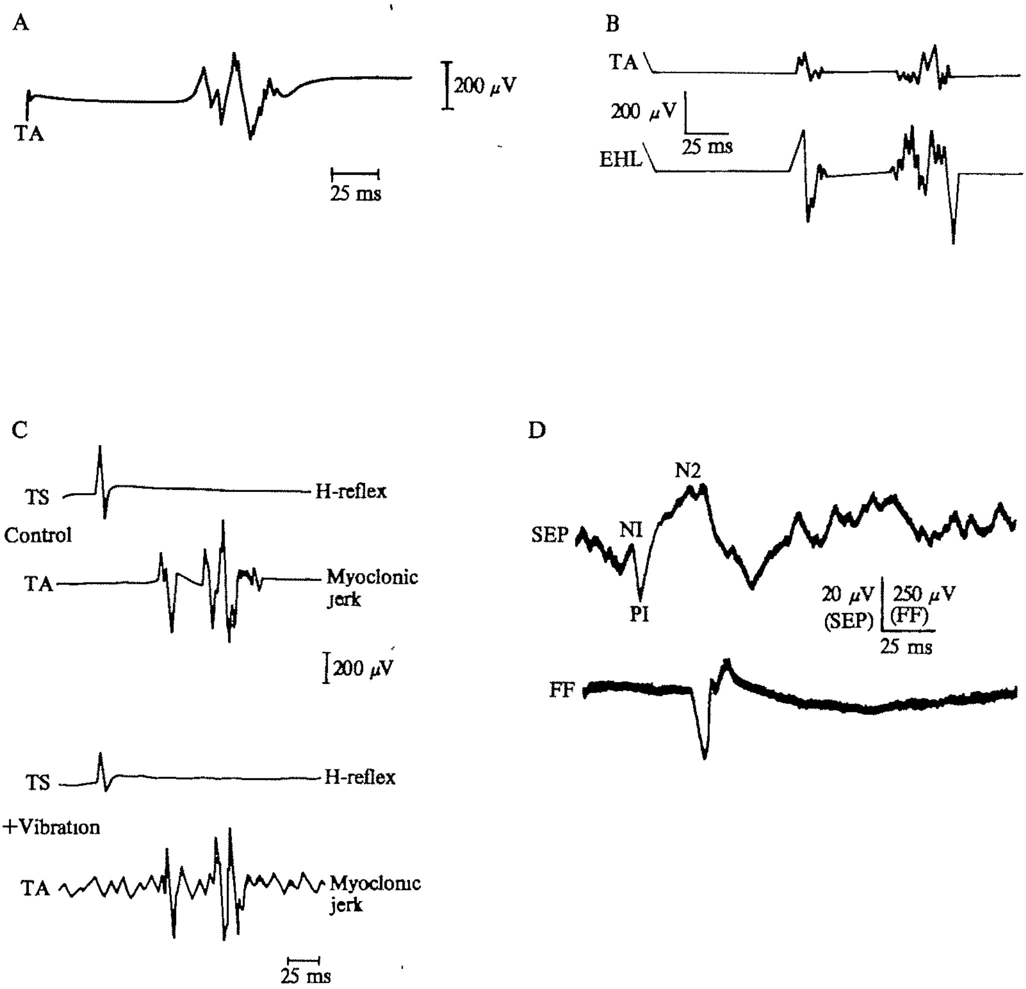


FIG. 2. *Case 1.* A, EMG recording from surface electrodes over right tibialis anterior (TA) showing average of 8 responses to light touch of the external aspect of the great toe at the start of the sweep. Latency to the onset of the response is about 80 ms. B, single EMG record from surface electrodes over tibialis anterior (TA) and from needle electrodes in extensor hallucis longus (EHL) showing 'doublet' response to a single electrical stimulus to the great toe *via* ring electrodes at the start of the sweep. The initial EMG burst has a latency to onset of 85 ms, the second of 145 ms. C, effect of Achilles tendon vibration at 60 Hz on the H-reflex in triceps surae (TS) and on the reflex myoclonic jerk in tibialis anterior (TA). H-reflexes produced by electrical stimulation of the tibial nerve, and myoclonic jerks caused by electrical stimulation of the great toe at the start of the sweep. The upper pair of records shows the responses without vibration, the lower pair the responses to the same stimulation parameters in the presence of tendon vibration (note a.c. artefact on TA lower record). The myoclonic response in TA is unaffected by vibration, whereas the H-reflex is halved in size. Traces are the average of 8 responses. D, SEP (Average of 64 responses) from contralateral hand area and myoclonic muscle jerks in right flexor carpi radialis (FF), following electrical stimulation of the digital nerves of the right thumb with ring electrodes. Stimulus given at the start of sweep. The interval between the P1 SEP peak and the onset of the EMG response is 18 ms.

The EMG records in this fig (and those in figs. 3 and 4) were recorded on UV paper and have been retouched by hand for clarity.

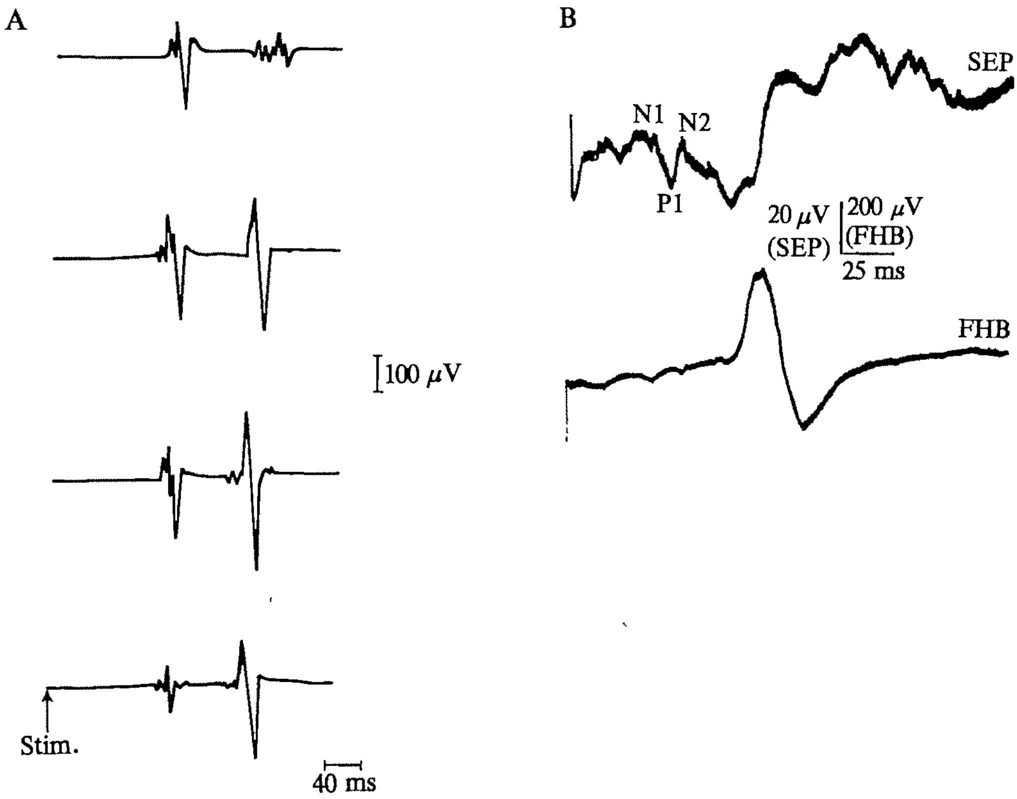


FIG. 3. *Case 2.* A, four single reflex myoclonic jerks in flexor hallucis brevis following an electrical stimulus given to the belly of tibialis anterior *via* a needle electrode at the start of the sweep. Stimulus intensity was sufficient to evoke a small direct muscle twitch of tibialis anterior. Latency to the onset of the first EMG response is about 80 ms, whereas the second is at about 160 ms. B, SEP (average of 128 responses) from leg area of somatosensory cortex (2 cm posterior to vertex: *upper trace*) and reflex muscle jerks in flexor hallucis brevis (FHB), following electrical stimulation of tibialis anterior through a needle electrode at the start of the sweep.

extensors and flexors of the toes following either form of stimulation. The latency to onset of the first burst was about 80 ms (fig. 3A). The second EMG discharge, if present, occurred with an onset latency of about 160 ms. These stimuli evoked no such EMG events in tibialis anterior or the muscles of the calf. Cutaneous electrical stimulation of the anterolateral portion of the leg did not induce a muscle jerk.

SEPs were recorded from electrodes over the somatosensory foot area (2 cm posterior to the vertex) after tapping the sensitive region, or after stimulation *via* needle electrodes placed in tibialis anterior. The latency to the peak of the first positive component was 40 ms following electrical stimulation, and the amplitude of the P1-N2 component was 20 μV (fig. 3B).

Cutaneous, Stretch and Visual Reflex Myoclonus

Case 3. P.R.L. (Clinica Universitaria No. 73247), a 67-year-old lady who had been diagnosed as having Parkinson's disease in 1971. Her parkinsonian features improved considerably with L-DOPA treatment (1 g/day). In 1974, therapy with L-DOPA plus benserazide (600/150) was begun. A year later end-of-dose deterioration became apparent and over the following three years her disability increased despite additional treatment with bromocriptine and amantadine. By 1980 she could no longer walk unassisted. She was unable to swallow solid food and her speech became severely impaired. When examined in 1983, withdrawn from antiparkinsonian medication, she was bed-bound, unable to speak, and severely akinetic and rigid. Tendon jerks were exaggerated and the right plantar response was extensor. The EEG showed generalized slow theta activity. A CT scan showed considerable atrophy of the brainstem and cerebellar vermis with moderate cerebral cortical atrophy. A clinical diagnosis of olivopontocerebellar atrophy was made.

When withdrawn from drugs, light touch, pin-prick to the palmar surface of the fingers and the plantar surface of the toes (fig. 1C, D), or tapping the wrist or toes with a tendon hammer provoked repetitive muscle jerks localized to the stimulated limb. In the arm these were characterized by flexion of fingers, wrist and elbow; in the leg by flexion of the toes, and sometimes extension of the great toe. Pin-prick of the medial plantar region of either foot also produced dorsiflexion of the foot. Threatening visual stimulation evoked a generalized myoclonic jerk. There were no jerks at rest and voluntary movement did not cause myoclonus.

She was discharged on treatment with oral lisuride (3 mg/day) and Sinemet 275 (4 tablets/day), but died several months later of aspiration pneumonia.

Physiological studies. Electrical stimulation of either thumb elicited a large SEP over the contralateral sensorimotor cortex with a latency to the peak of the first positive component of 28 ms and an amplitude of P1-N2 of 25 μV. Such digital nerve stimuli also caused a reflex muscle jerk in the finger and wrist flexors with a latency of 50 ms. This initial brief (10–20 ms) EMG discharge often was followed by 2 to 3 later bursts, at intervals of 20 to 30 ms. Electrical stimulation of the toes did not trigger myoclonus. However, taps to the plantar surface of the great toe evoked a brief (40 ms) contraction of tibialis anterior with a latency to the onset of the EMG burst of 80 ms. (These findings are similar to those in Case 1 so are not illustrated.) Visual evoked responses (VERs) to flash stimulation recorded from over the occipital cortex at the external occipital protuberance were studied when the patient was on and off L-DOPA therapy. When she was off medication, VERs to flash stimulation at a frequency of 2 Hz were increased in amplitude, but there were no muscle jerks. The first positive peak, with onset some 30 ms after flash had an amplitude of 50 μV. When the flash frequency was increased to 3 Hz, each flash was followed by a generalized muscle jerk (fig. 4A). The interval between the first positive peak of the VER and the onset of the EMG discharge recorded from biceps brachii was 30 ms (fig. 4B, top). This was some 12 ms longer than the interval between peak of the P1 component of the electrically-evoked SEP and the onset of the EMG burst causing the reflex jerk in the same muscle (fig. 4B, bottom). When L-DOPA (Sinemet 275 4 tabs/day) medication was restored she no longer exhibited flash-evoked myoclonus and the VERs were of normal amplitude. Myoclonus induced by digital nerve stimulation was not affected by this treatment. Lisuride (0.15 mg i.v.) abolished the somaesthetic reflex jerks. Flash-evoked jerks could not be tested.

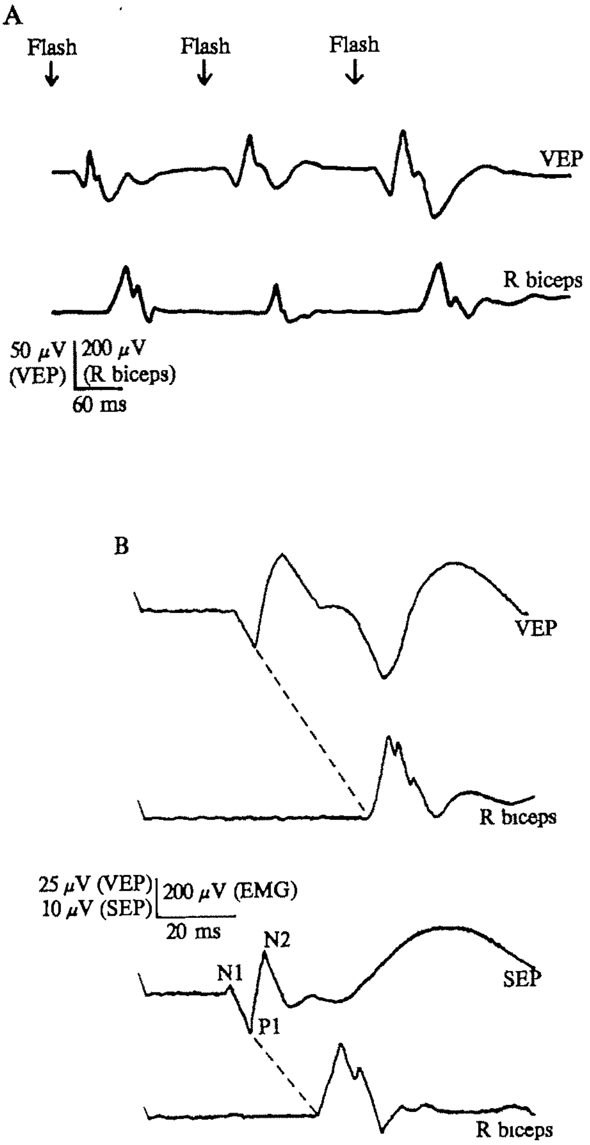


FIG. 4. *Case 3.* A, section of a continuous record showing visual evoked responses (VEP), recorded from an electrode over the occipital cortex, and surface EMG potentials from the right biceps brachii (R biceps) following flash stimulation at a frequency of 6 Hz. Each flash (shown by arrow) was followed by a very large VEP (50 μV), clearly visible in the ongoing EEG, and a later generalized muscle jerk. B, comparison between the SEP and reflex muscle jerk following visual stimulation at 3 Hz (*upper records*) and electrical stimulation of the digital nerves of the right index finger (*lower records*) delivered at the start of the sweep. EEG records are from an electrode placed 5 cm above the inion, referred to the vertex (VEP) and from an electrode over the contralateral somatosensory hand area, referred to linked mastoid electrodes (SEP). Both forms of stimuli evoke large cerebral potentials of similar shape. However, the interval between the P1 component of the VEP and the muscle jerk in the biceps brachii muscle (30 ms) is some 12 ms longer than that between the P1 peak of the SEP and the onset of the muscle jerk (18 ms) following digital nerve stimulation (dotted lines).

Pure Isolated Action Myoclonus

Case 4. J.A. (Maudsley Hospital No. 833508), a 27-year-old woman with an eight-year history of muscle jerking. Her neurological symptoms began in 1965 when she experienced a grand mal convulsion. This was one year after suffering head trauma in a road accident after which she was unconscious for a few minutes. There was no amnesia or any other significant complication. Past history, including pregnancy and birth, was unremarkable There was no family history of neurological disease.

From 1967 to 1975 she experienced occasional falling attacks, without loss of consciousness, some of which were provoked by unexpected loud noises. She was treated initially with phenobarbitone and ethosuximide. In 1975 she was admitted to hospital because of myoclonic jerking and unsteadiness of gait. At that time generalized action myoclonus prevented her from walking unaided, feeding herself, dressing and performing many other everyday activities. In addition she had a mild cerebellar ataxia. She had been treated with clomipramine, L-tryptophan without carbidopa, ethosuximide, methsuximide, clonazepam, sodium valproate and primidone with little improvement in the myoclonus and ataxia.

When we first saw her in 1983, she was unable to walk alone. Her gait was wide-based and frequently interrupted by myoclonic jerking. Hypermetric saccades of horizontal eye movements were observed. There was no myoclonus at complete rest, nor could jerks be provoked by any external stimulation. Voluntary movement of the limbs precipitated a salvo of generalized muscle jerking. In addition she had myoclonus of the face and tongue during speech. The possible existence of limb dysmetria could not be evaluated because of the severity of the action myoclonus. The optic fundi, tendon jerks and plantar responses were normal. The remainder of the neurological and physical examination was normal. The routine EEG, CT scan and other investigations were normal. A diagnosis of dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome) was made.

Lisuride (0.1 mg) was administered i.v. whilst the patient was taking clonazepam (2 mg at night) and primidone (250 mg thrice daily). Twenty minutes after injection, there was a dramatic improvement in her action myoclonus. She could make independent finger movements, perform finger-nose and heel-shin testing, and could stand unassisted. The mild cerebellar ataxia of gait was still present. Some myoclonus was still evident, particularly in proximal muscles around the mouth, but generalized jerking was abolished. She was sent home on lisuride (1 mg), clonazepam (2 mg), primidone (25 mg) all thrice daily, and clomipramine (250 mg at night). Under this regime a considerable improvement of the action myoclonus was maintained.

Physiological studies. The EMG counterpart of the action myoclonus was characterized by multiple repetitive bursts of high-frequency hypersynchronous potentials occurring simultaneously in all active muscles (fig. 5A). The duration of each burst was extremely brief (< 20 ms). Tapping with a tendon hammer, or passive wrist displacement to stretch the finger and wrist flexor muscles, did not elicit any myoclonic jerks. Electrical stimulation of the digital nerves of either forefinger with ring electrodes produced an enlarged P1-N2 component of the SEP (20 μV), with a latency to the peak of P1 of 27 ms, over the contralateral sensorimotor area, without accompanying reflex muscle activation (fig. 5C). The EEG activity preceding small jerks recorded from the wrist and finger flexor muscles was back-averaged while one hand was held outstretched. A positive-negative spike was evident, maximal over the contralateral sensorimotor cortex, the positive peak of which preceded the muscle jerk by 20 ms (fig. 5B).

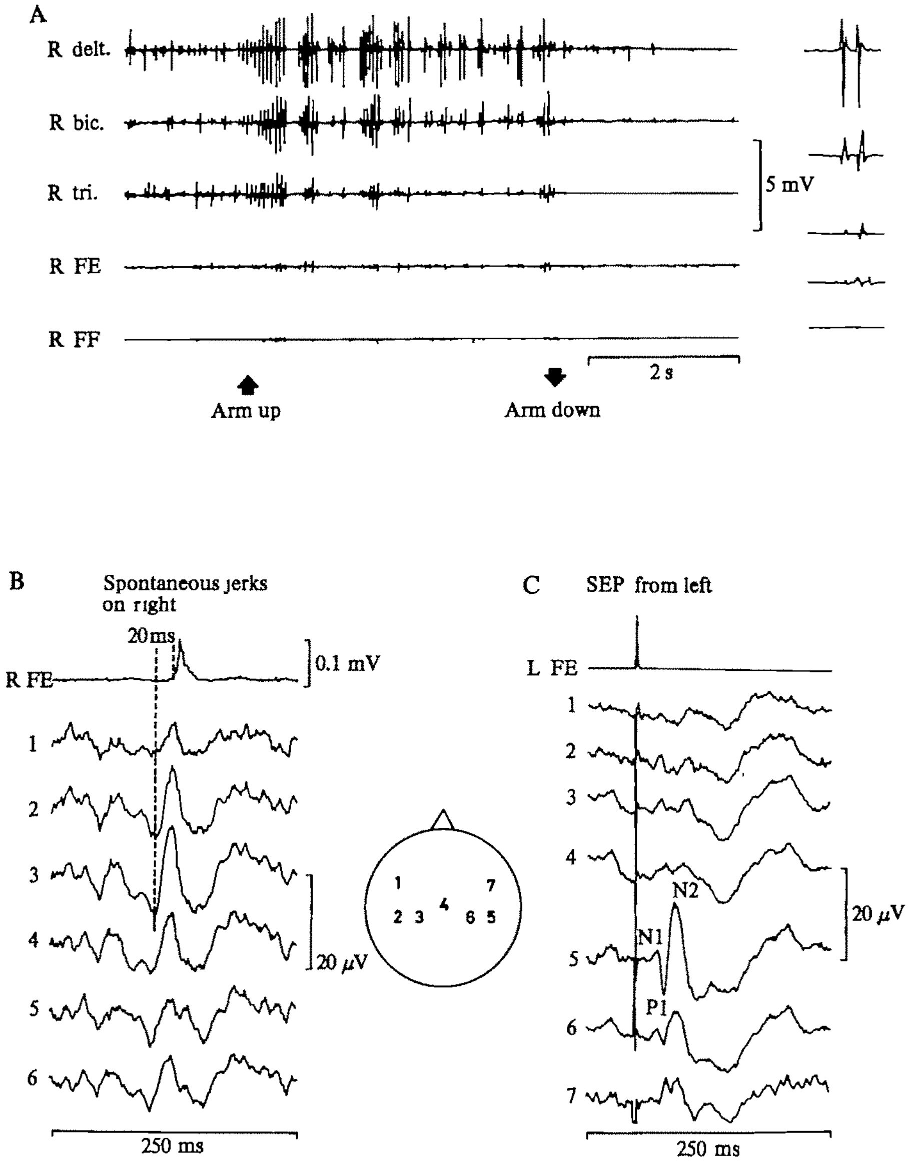


FIG. 5. *Case 4.* A, section of continuous EMG record showing general form of jerks on the right, when the arm is lifted up from rest. Muscles are deltoid (delt.), biceps brachii (bic.), triceps brachii (tri.), extensor muscles in the forearm (FE) and flexor muscles in the forearm (FF). The insert on the right illustrates the jerks in more detail. B, back-average of 70 EEG potentials preceding action-induced jerks of the extensor muscles of the right forearm (FE). A positive wave over the contralateral hemisphere precedes the onset of the jerk by 20 ms (dotted lines). Electrodes 2 and 5 are placed over the somatosensory hand areas, and electrode 4 at the vertex, referred to a linked mastoid reference. C, SEP (average of 128 responses) following electrical stimulation of the digital nerves of the left index finger. There is no reflex muscle jerk in the forearm muscles, although a large localized, contralateral potential is present.

Action and Cutaneous Reflex Myoclonus

Case 5. C.G. (Clinica Universitaria No. 122081), a 67-year-old lady with a four-year history of myoclonic jerking. There was no previous history of neurological disease or drug intake, and no history of any similar illness in her family. The symptoms began insidiously with occasional falls and difficulty in walking. Subsequently, other daily activities including eating, drinking, dressing and writing were impaired.

On examination in 1982, there was no myoclonus at rest, but any attempted voluntary action provoked myoclonus. The jerks were limited to the muscles activated, and particularly involved proximal muscles. Only rarely was there generalized myoclonus. Tendon taps, light touch or pin-prick to any part of the body, did not elicit reflex myoclonic jerks as judged by clinical observation. However, electrical stimulation of the digits provoked reflex myoclonus (*see below*). Jerks were not provoked by visual or auditory stimuli. Walking was very difficult because of the jerks, although she could walk unassisted for 2 to 3 yards. There was no evidence of limb dysmetria. The optic fundi, eye movements, tendon jerks and plantar responses were normal. The patient was started on treatment with clonazepam (2 mg twice daily) and sodium valproate (200 mg four times daily). There was a marked improvement in the myoclonus, allowing the patient to walk long distances and perform all normal daily tasks. However, an ataxic wide-based gait became evident, and a postural tremor of the upper limbs developed over the following months, and did not disappear when sodium valproate was withdrawn for two weeks. All investigations were normal. A tentative diagnosis of dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome) was made.

Lisuride (0.1 mg i.v.) dramatically reduced the reflex jerks. Clonazepam (1 mg i.v.) also reduced the reflex muscle discharge. Action myoclonus only improved moderately after either drug. Subsequently, the patient was treated with clonazepam (4 mg per day) with only a slight improvement. The addition of sodium valproate (1200 mg per day), however, resulted in a considerable resolution of the action and reflex jerks. When clonazepam subsequently was reduced to 2 mg per day, the myoclonus worsened again. She was finally discharged on a combination of both drugs.

Physiological studies. All physiological studies were performed before the postural arm tremor appeared. Movement of a limb provoked EMG discharges consisting of brief (50–60 ms) sometimes repetitive bursts of activity, occurring simultaneously in antagonist muscles. Electrical stimulation of the digital nerves of either forefinger with ring electrodes produced an enlarged P1-N2 component of the SEP (25 μV) over the contralateral sensorimotor cortex. This was followed by a reflex muscle jerk in the finger and wrist flexors with a latency of 46 ms, even although light manual touch had failed to provoke myoclonus. These findings were very similar to those in Case 4, so are not illustrated. Simultaneous recording of EEG and EMG events did not show any correlation. Back-averaging of the EEG activity preceding the muscle jerks could not be performed.

Action, Cutaneous and Stretch Reflex Myoclonus

Case 6. J.M. (Maudsley Hospital No. 802262), a 69-year-old man with a two-year history of jerks affecting the right hand. There was no past or family history of neurological disease. He had not been on any drug treatment, other than a diuretic for mild hypertension. Symptoms developed gradually until he could no longer use the right hand in daily life because of the continuous jerking.

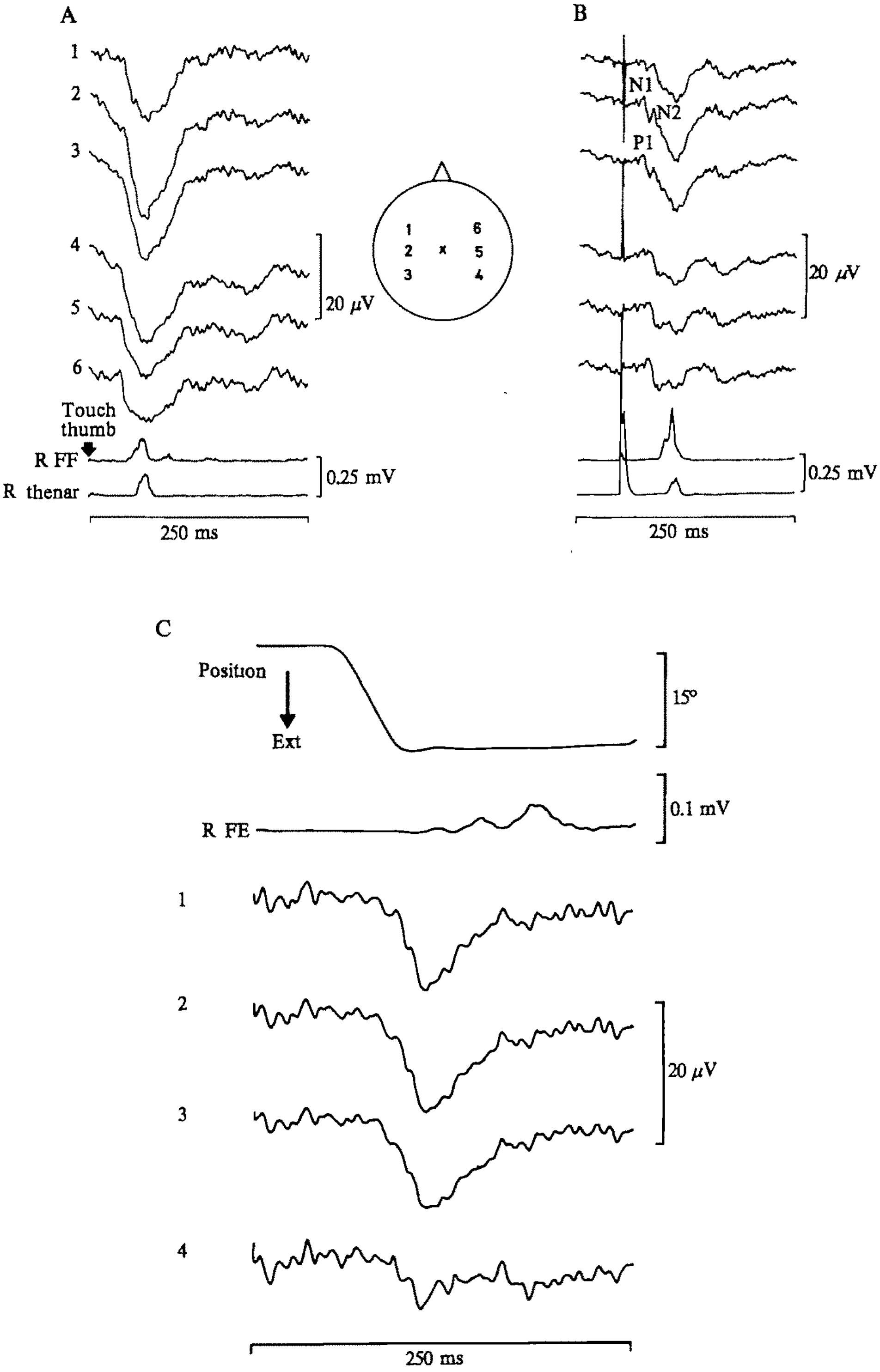
On examination in 1980, there was no myoclonus at rest, but on the slightest action there was repetitive irregular myoclonus affecting the flexor and extensor muscles of the right forearm. The slightest tactile stimulation of palmar or dorsal surfaces of the fingers or hand (fig. 1E, F), and tapping the fingers or wrist with a tendon hammer, triggered a series of muscle jerks. The hand was held with the fingers flexed at the metacarpophalangeal and proximal interphalangeal joints. Both the myoclonus and flexion posture of the hand disappeared during sleep. There was no sensory impairment of the hand; motor power could not be tested owing to the abnormal posture of the fingers and the myoclonic jerking. The rest of the neurological examination was normal except for mild blepharospasm.

By June 1981, the right hand myoclonus and flexion posture of the fingers was unchanged. However, a mild anomic dysphasia accompanied by memory loss and reduction in IQ had developed. In the next two years, intellect declined markedly and the patient became bed-bound. At this time a CT showed discrete cortical-subcortical atrophy and ventricular enlargement. All routine diagnostic tests were normal, apart from the EEG which showed theta activity intermittently in runs over the centro-temporal regions of the left hemisphere. The aetiology of this patient's encephalopathy was never discovered.

Lisuride (0.1 mg i.v.) considerably decreased the severity of reflex jerking, and, to a lesser extent, the action myoclonus. The flexion posture of the fingers remained unchanged. The patient received oral treatment with valproate (400 mg thrice daily), clonazepam (2 mg twice daily) and carbamazepine (200 mg four times daily) given either independently or in combination which gave no benefit.

Physiological studies. EMG recording from the forearm flexor and extensor muscles and from the thenar muscles of the right arm showed repetitive but arrhythmic bursts of muscle discharge each lasting 25 to 50 ms, which were synchronous in all muscles (similar to the record shown in fig. 5A). EMG responses elicited by light touch to the thumb or fingers, or by stimulation of the digital nerves of the thumb by ring electrodes consisted of one to three repetitive bursts of muscle activity, each lasting 20 to 40 ms (fig. 6A, B). The latency to the onset of the initial EMG discharge was 50 ms; later discharges followed with a period of 30 to 40 ms. EMG responses evoked by tapping with a tendon hammer the thumb, finger or wrist, or by passively flexing the wrist with a torque motor, consisted of two or three similar bursts of activity (fig. 6C). The initial components of the cortical SEPs to digital nerve stimulation of the right thumb were normal (fig. 6B). However, following the N2 wave there was a large abnormal positive wave, with onset before the myoclonic jerk, the interval being only 10 ms. Touch of the pad of the right thumb (fig. 6A), or stretch of the wrist extensors (fig. 6C) caused a similar abnormal large delayed positive wave. With all stimuli, this abnormal positive wave was maximal over the contralateral hemisphere. Back-averaging of the EEG preceding the EMG bursts responsible for the action myoclonus in the finger and wrist flexor muscles did not reveal any time-locked brain activity.

FIG. 6 (*opposite*). *Case 6*. SEPs and reflex muscle jerks in the flexor muscles of the right forearm (FF) and right thenar muscles (thenar), following light touch of the right thumb pad (A), electrical stimulation of the digital nerves of the thumb (B), and forcible extension of the wrist with a torque motor (C). All three types of stimulation produced myoclonic jerks, even in the shortened extensor muscles of the forearm (FE) when the wrist was passively extended (C). The initial (P1, N1, P2) response to electrical stimulation (B) is not large, but is followed by a later slow positive wave which is maximal contralaterally. The same potential is present following all three types of stimulation. Traces are the average of 128 trials Electrodes 3 and 4 are over the somatosensory hand area.


A
1
2
3
4
5
6
20 μV
Touch thumb
R FF
R thenar
0.25 mV
250 ms
1
6
2
x
5
3
4
B
N1
N2
P1
20 μV
0.25 mV
250 ms
C
Position
Ext
15°
R FE
0.1 mV
1
2
3
4
20 μV
250 ms

Action, Cutaneous, Stretch and Visual Reflex Myoclonus with Epilepsy

Case 7. J.D. (Clinica Universitaria No. 167360), a 15-year-old girl with a history of epilepsy and action myoclonus. Pregnancy and birth were normal; there was no family history of neurological disease. She had a normal psychomotor development until the age of 3 yrs, when she began to have simple absence seizures, followed a few months later by generalized tonic-clonic convulsions. No EEG records from this time are available for review. She was treated with a variety of antiepileptic drugs including hydantoin, ethosuximide, troxidone, and sodium valproate. About this time grand mal seizures occurred up to 10 times per week. At the age of 11 yrs, she experienced walking difficulties, which were followed within the next one to two months by gross generalized muscle jerking on voluntary action. She was treated with clonazepam (10 mg/day), with transient improvement of the mycolonus, and the incidence of epileptic seizures decreased considerably (1-2 times per week). Interestingly, her family observed a consistent and dramatic reduction in myoclonus for 1 to 2 days after a generalized convulsion They also volunteered a marked sensitivity to visual stimuli: for example she would have a series of jerks when exposed to sudden changes in light intensity such as experienced when a light was turned on in a dark room.

On examination in 1983, a marked right-sided convex scoliosis and pes cavus were evident. Intelligence was normal. There was no muscle jerking at rest, but any attempt at voluntary movement provided a series of repetitive and generalized muscle jerks. She was unable to walk, drink, feed herself, or perform any other simple motor tasks. Speech provoked jerks in the bulbar muscles. Light touch, pin-prick or tapping with a tendon hammer did not evoke any obvious myoclonic jerks. However, electrical stimulation of the fingers caused myoclonus (*see below*). It was not possible to judge whether there was any limb ataxia. Ataxia of gait was observed after appropriate drug therapy (*see below*). The remainder of the neurological examination was normal. The EEG showed normal background activity interrupted by fast generalized polyspikes predominant over the rolandic regions. Brief bursts of spike and wave activity (3 Hz) were recorded during overbreathing. A CT scan showed slight cerebellar vermis atrophy. A diagnosis of dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome) was made.

Lisuride (0.1 mg i.v.) induced a dramatic improvement in the action and somaesthetic reflex myoclonus, with little effect on the photomyoclonic response. Proximal muscle jerking was particularly suppressed. Apomorphine (1 mg, s.c.) produced no change in the somaesthetic reflex myoclonus, a moderate reduction in action myoclonus, and suppression of the flash-evoked jerking. Infusion of 5-hydroxytryptophan (180 mg i.v.) with carbidopa (75 mg orally) over 90 min abolished the somaesthetic reflex myoclonus and produced a marked improvement of the action myoclonus. Unfortunately, the photic myoclonic responses after infusion could not be evaluated due to vomiting. Oral treatment with clonazepam (2 mg thrice daily) and sodium valproate (300 mg thrice daily) resulted in a marked reduction in myoclonus. One week later, primidone (250 mg at night) was added with further improvement. The patient could now walk for long distances and carry out all normal daily motor tasks. At this time ataxia of gait became evident.

Physiological studies. The action-induced jerks were characterized by a series of brief (10-20 ms) EMG discharges, synchronous in all muscles involved. Back-averaging of the EEG activity could not be performed. Electrical stimulation of the digital nerves of either forefinger with ring electrodes produced a large SEP localized over the contralateral sensorimotor area. The latency to the peak of P1 was 24 ms, and the amplitude of P1-N2 was 40 μV. This was followed by a reflex muscle jerk in the finger and wrist flexors with a latency of 42 ms. Stretching flexor pollicis longus evoked a similar large SEP and muscle jerk with the same latency. Flash-evoked VEPs at 1 Hz were normal, but when flash frequency was increased to 7 Hz, bilateral upper limb myoclonus began. After 10 s of stimulation a myoclonic storm developed, which ceased as soon as the flashing stopped. These findings were similar to those in Case 4 with regard to the action and somaesthetic myoclonus, and to Case 3 with regard to the visual myoclonus, so are not illustrated.

Spontaneous, Action, Cutaneous and Stretch-sensitive Reflex Myoclonus and Epilepsy

Case 8. E.A. (Maudsley Hospital No. 722647). This case was reported previously by Hallett *et al.* (1979). Only a brief summary will be given here. A 55-year-old woman sustained a severe head injury in 1949. After the accident she remained unconscious for three days, although no episodes of hypoxia were recognized. For the following two years she had grand mal seizures, but subsequently had only occasional right-sided focal motor seizures. Immediately after regaining consciousness, she had had a number of generalized myoclonic jerks. These gradually developed over the next twenty years into a severe action myoclonus. In 1974 she responded dramatically to treatment with 5-HTP, but gastrointestinal side-effects precluded long-term treatment with serotonin pecursors. Clonazepam (up to 14 mg daily) also improved the myoclonus and she was maintained on this drug, together with primidone (250 mg thrice daily) to prevent the seizures which had begun to recur. CT scan was normal, but the EEG was dominated by generalized low voltage beta activity (20-24 Hz). Irregular bursts of diffuse spike and wave and polyspike and wave activity were recorded. A diagnosis of posttraumatic myoclonus was made (*see* Hallett *et al.*, 1979).

During 1981 she was troubled increasingly with falls and jerky movements of the limbs and face. She was admitted whilst on treatment with clonazepam (2 mg four times daily), primidone (250 mg twice daily), and clomipramine (25 mg twice daily). There was frequent myoclonic jerking of the bulbar musculature which interfered with, and was precipitated by speech. At complete rest, there were frequent myoclonic jerks of the limbs and particularly the proximal muscles. Any attempt at voluntary movement provoked a series of jerks in the limb being moved and often gave rise to generalized jerking of the whole body. Tapping a limb with a tendon hammer, or light touch or pin-prick applied to the hands and forearm, did not elicit any obvious clinical jerks. However, electrical stimulation of the digits or stretch of the long thumb flexor caused myoclonus (*see below*). Gait was wide-based and unstable. Falls occurred because of positive myoclonic jerks, rather than because of pauses in the activity of leg muscles.

She was readmitted in October 1981, when clonazepam was discontinued, leading to a marked increase in the frequency and severity of myoclonus. Injection of lisuride (0.15 mg i.v.) resulted in a dramatic improvement of the action myoclonus, although some proximal muscle jerks remained. Clonazepam was reintroduced at a lower dosage and sodium valproate added to the regime until a maximum intake of (1200 mg/day) was reached. Once stabilized on this dosage, clonazepam was discontinued again, but the jerks greatly increased. Finally, she was discharged on clonazepam 6 mg/day, sodium valproate 1200 mg/day and primidone 500 mg/day. When reviewed one month later, the myoclonus had disappeared almost completely both when at rest or upon action. She was able to carry out many motor acts such as dancing or writing without difficulty. Speech was no longer affected by muscle jerks. The improvement has persisted until the present time, about two years later.

Physiological studies. The results of the physiological investigations in this patient have been illustrated in Hallett *et al.* (1979), so only a summary of the findings will be presented.

The EMG correlate of spontaneous and action-induced jerking was a short (20-50 ms) burst of activity, synchronous in antagonist muscles. Multiple bursts occurred with a period of 30-50 ms. In generalized jerks, muscles were activated with a rostrocaudal order.

There seemed to be a loose association between spike and wave complexes in the EEG and EMG discharges from the arm muscles. Back-averaging the EEG activity preceding jerks of the finger and wrist flexors revealed a large (20 μV) positive-negative spike localized over the contralateral sensorimotor cortex. The positive peak preceded the jerk by 17 ms.

SEPs recorded following electrical stimulation of the digital nerves of either forefinger with ring electrodes had an amplitude of 10 μV(P1-N2 component) while she was on treatment. During withdrawal of medication, SEPs increased in size to 25 μV. The latency to the peak of the first positive component was 30 ms. This was followed by a series of EMG discharges in the finger and wrist flexors and extensors. The latency to the onset of the initial EMG burst was 45 ms; later components arose with an interval of 40 ms. Stretching the flexor pollicis longus with a torque motor also revealed reflex myoclonus and large evoked cortical responses which did not disappear after thumb anaesthesia (*see* Hallett *et al.*, 1979).

Spontaneous, Action and Reflex Myoclonus with Epilepsia Partialis Continua

Case 9. J.B. (Maudsley Hospital No. 811436), a 33-year-old woman with a three-year history of repetitive jerking of the right hand. There was no previous or family history of neurological disease other than very occasional migraine attacks. Symptoms began with clumsiness of the right hand during tasks requiring delicate finger movements. A few weeks later, any hand movement triggered off repetitive muscle jerking. Subsequently the myoclonus also occurred at rest. At about this time she had two grand mal seizures, and was started on phenytoin and clonazepam. On examination in 1981 she exhibited continuous, spontaneous, repetitive flexion jerks of the fingers of the right hand. Tapping the fingers or wrist with a tendon hammer, or light touch or pin-prick of the fingers (fig. 1G), provoked a massive jerk of the whole arm. The most sensitive triggering area was on the palmar surfaces of the tips of thumb and fingers, although jerks could be elicited by stimulation of any other part of the hand. Voluntary movement of the right arm exacerbated the jerking. The hand and forearm were held in a posture of flexion (fig. 7A). She was unable to use the hand for any manual task. There was no sensory loss, and motor power, so far as could be judged, was normal. Tendon jerks appeared symmetrical and normal. The rest of the neurological and general physical examination was unremarkable. EEGs showed repetitive spikes over the left rolandic region. Several CT scans (with enhancement) and left carotid angiography were normal. The pathological diagnosis of a left hemisphere lesion remains undetermined.

Lisuride (0.1 mg i.v.) produced a prominent reduction in the spontaneous, action and reflex muscle jerking, unfortunately accompanied by extreme nausea and vomiting. Subsequently, she was treated with clonazepam (2 mg twice daily) while phenytoin was kept at the usual dose of 300 mg/day. She could not tolerate addition of valproate (300 mg thrice daily). Primidone (250 mg thrice daily) was added, resulting in a dramatic improvement of the jerks and flexion posture of the right hand. The patient was then able to execute fine finger movements and could employ her right hand in normal daily activities. Clonazepam was reduced temporarily to 2 mg nightly but the myoclonus worsened. Improvement was sustained thereafter for the next year of follow-up.

Physiological studies. The EMG correlate of the spontaneous myoclonus of the right arm was characterized by arrythmic but repetitive bursts (25–50 ms) of muscle activity at about 4 to 5 Hz. The discharges were synchronous in all hand and forearm muscles (fig. 7B).

Back-averaging of the EEG revealed a large (40 μV) positive-negative spike over the left sensorimotor cortex, the positive peak of which preceded the muscle jerks in the finger and wrist flexors by 22 ms (fig. 7C).

Electrical stimulation of the digital nerves of the right forefinger with ring electrodes, or stretching flexor pollicis longus with a torque motor, evoked a large SEP localized to the left sensorimotor cortex (fig. 7D, E), followed by muscle jerks. The latency to the peak of P1 was 30 ms, and the P1-N2 amplitude was 30 μV. The initial P1-N2 was followed by another similar positive-negative wave 25 to 30 ms later. The reflex muscle jerk also consisted of two components separated by 25 to 30 ms with an initial onset latency of 52 ms. A second electrical shock 50 to 60 ms later could evoke a third large positive-negative SEP (fig. 7F), followed by a third muscle jerk.

Spontaneous and Action Myoclonus with Epilepsia Partialis Continua and Jacksonian Seizures

Case 10. F.M. (Atkinson Morley's Hospital No. J413335), a 60-year-old man presented with a four- to five-week history of low back pain, anorexia and weight loss. He was admitted in April 1981 after an episode of uncontrollable jerking of the left arm and leg which had lasted for a few minutes. A few hours later he suffered a generalized grand mal convulsion. On regaining consciousness he was left with persistent repetitive jerking of the dorsiflexor muscles of the left foot. These jerks sometimes spread proximally to involve the whole leg, the left arm and rarely the face. They were episodic, occurring every 15 to 30 min and lasted 1 to 4 min. There was no clinically obvious myoclonus to pin-prick or light touch of the left leg or to tendon taps applied to the knee or ankle. Motor power of the left limbs could not be assessed properly due to the persistent muscle jerking. Sensation was normal, as were the tendon jerks, and the plantar responses were flexor. There was horizontal nystagmus on lateral gaze in both directions. His temperature had been normal throughout. The rest of the neurological examination was unremarkable. The EEG showed slow and sharp waves particularly over the right frontotemporal region. CSF studies were performed on three occasions, and always showed a raised white cell count (17, 13 and 28 per mm^3; 95 per cent lymphocytes) with normal glucose and protein content. CSF cultures were negative. Two CT scans were reported as normal. Routine blood tests and chest and abdominal x-rays were normal. Treatment was begun with phenytoin (400 mg/day), carbamazepine (200 mg twice daily) and clonazepam (0.5 mg thrice daily) to which dexamethasone (8 mg i.m./day) was added. A clinical diagnosis of focal encephalitis was suspected. The patient's general condition subsequently deteriorated over the following days and he died in another hospital. Post-mortem studies could not be performed.

Physiological studies. The EMG correlate of the spontaneous muscle jerks consisted of irregular continuous bursts (lasting 50 ms or sometimes longer up to 200 ms) of muscle activity at about 0.5 to 1 Hz, synchronous in tibialis anterior, triceps surae, quadriceps and biceps femoris (fig. 8A).

There was no obvious correlation of the ongoing EEG activity with the muscle jerks. However, back-averaging demonstrated a large monophasic negative spike (20 μV) over the midline rolandic region, the onset of which preceded the jerks in the quadriceps muscle by 30 ms (fig. 8B). Electrical stimulation of the digital nerves of the left great toe with ring electrodes elicited a large negative wave in the SEP (10 μV) with a latency to peak of 40 ms (fig. 8C).

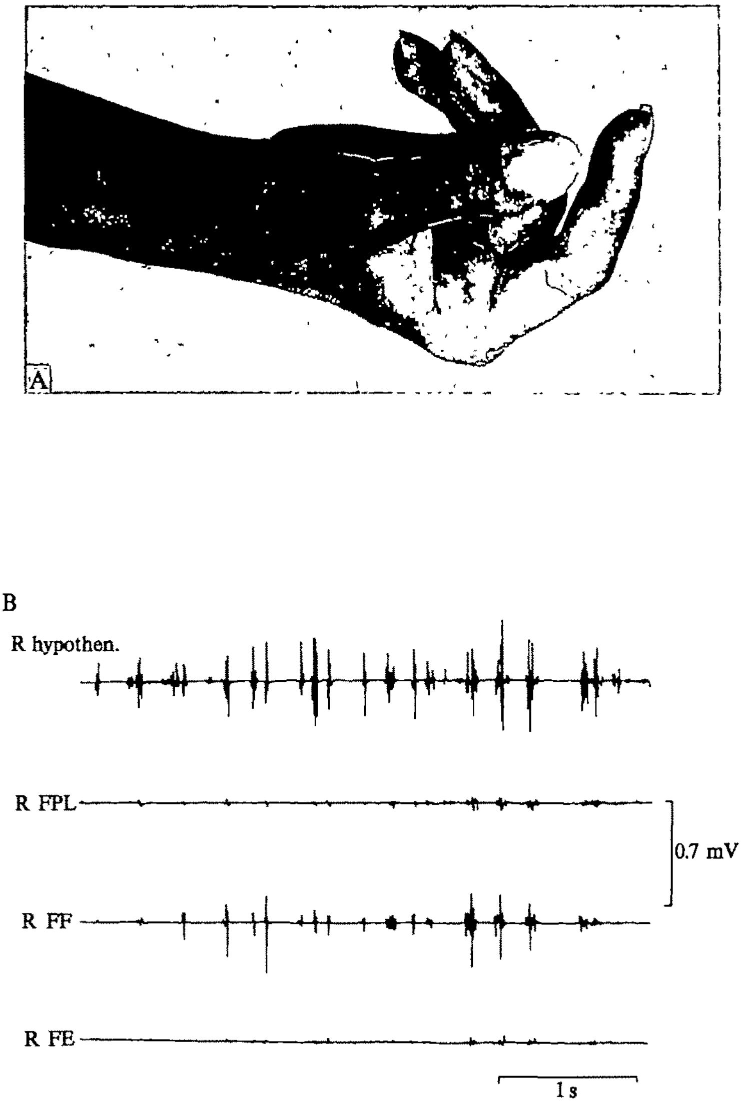
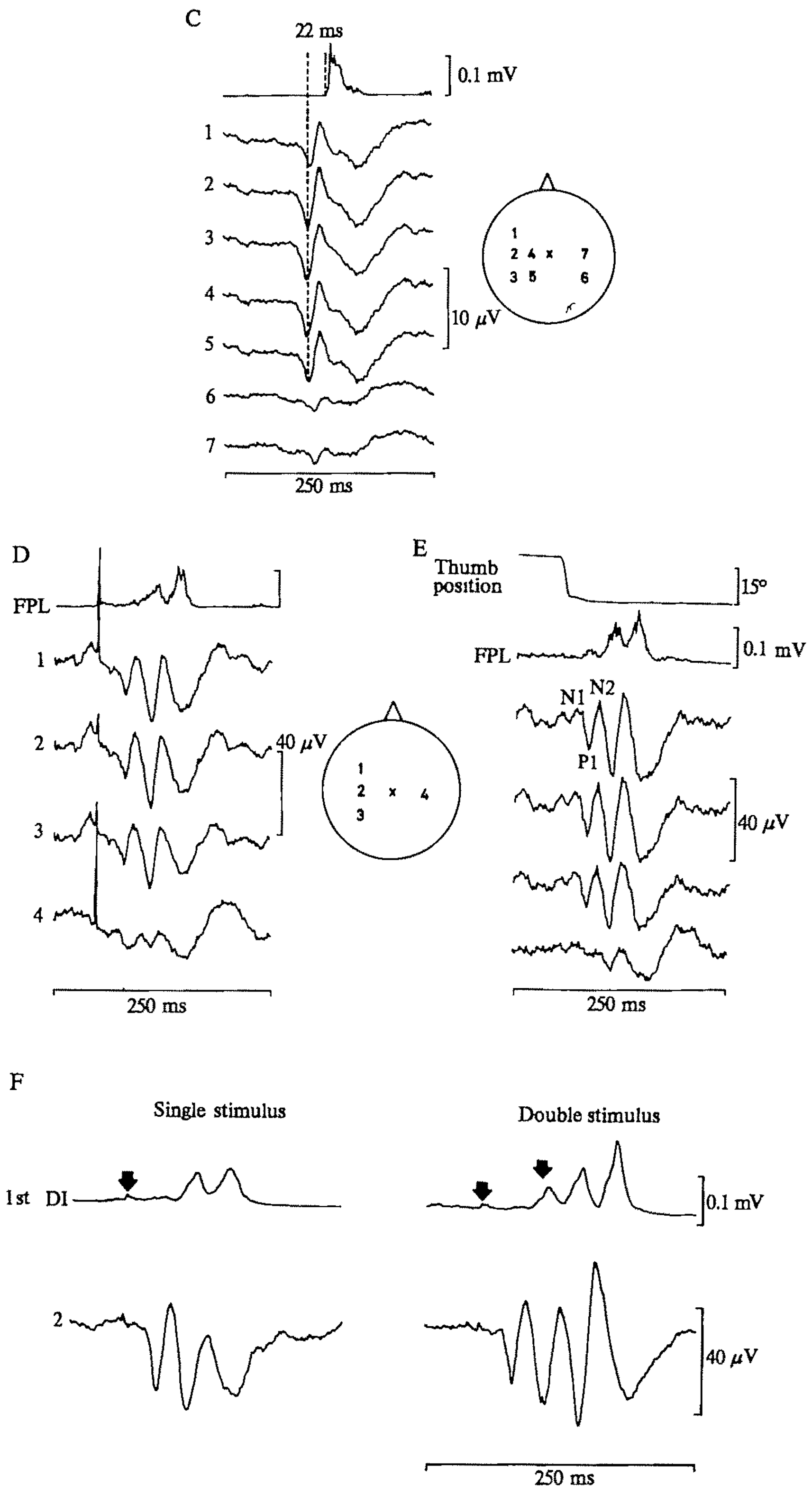


FIG 7. *Case 9.* A, permanent posture of hand. B, section of EMG record illustrating form of spontaneous jerks in right hand. Muscles are hypothenar (hypothen.), flexor pollicis longus (FPL), flexor (FF) and extensor (FE) muscles of the forearm. C, back-average of 120 EEG records showing contralateral positive potential preceding the onset of spontaneous jerks in the right hypothenar muscles by 22 ms. Electrodes 3 and 6 are over the somatosensory hand areas. D and E, SEPs (average of 32 responses) and muscle jerks in flexor pollicis longus (FPL) following electrical stimulation of the digital nerves of the thumb (D) or forcible extension of the terminal phalanx of the thumb while the patient was exerting a small background contraction against a steady torque of 0.06 Nm (E). A large contralateral evoked potential precedes the muscle jerk following either stimulus. F, ability of a second, closely-spaced electrical stimulus to the right thumb to evoke successive large cerebral responses and muscle jerks. Records on *left* show average of 64 responses to a single shock, records on *right* show average of 64 responses to a double shock given with an interval of 60 ms. Stimuli at arrows. Muscle response from right first dorsal interosseus (1st DI).


C
22 ms
0.1 mV
1
2
3
4
5
6
7
10 μV
250 ms
1
2 4 x 7
3 5 6
D
FPL
1
2
3
4
40 μV
250 ms
1
2 x 4
3
E
Thumb position
15°
FPL
0.1 mV
N1
N2
P1
40 μV
250 ms
F
Single stimulus
Double stimulus
1st DI
0.1 mV
2
40 μV
250 ms

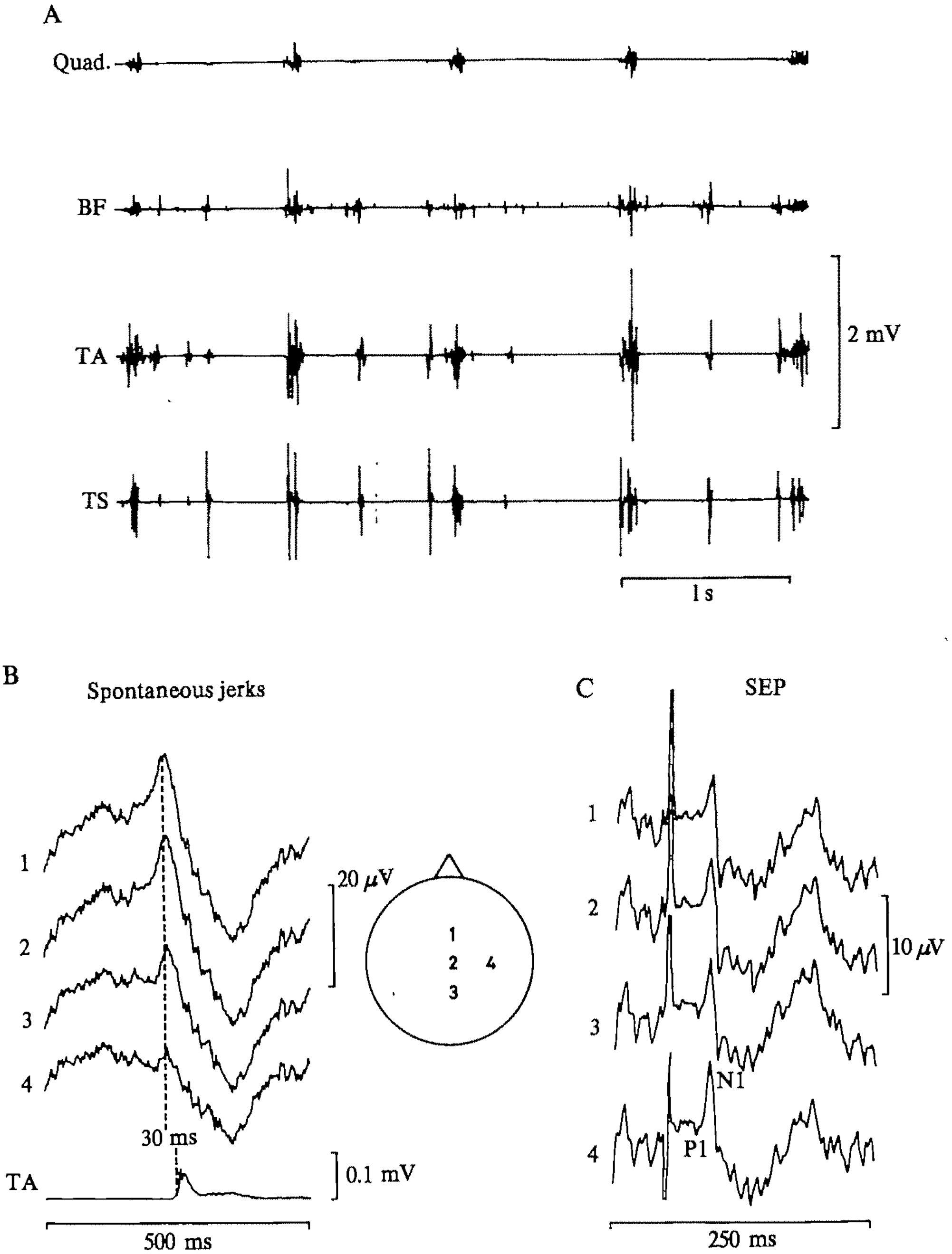


FIG. 8. *Case 10.* A, section of continuous record showing form of spontaneous muscle jerks in the left leg. Muscles are quadriceps (Quad.), biceps femoris (BF), tibialis anterior (TA) and triceps surae (TS). B, back-average of 128 EEG potentials preceding spontaneous jerk in left tibialis anterior. A large negative wave, maximal over the midline precedes the onset of the jerk by 30 ms (dotted lines) C, SEP (average of 192 responses) following electrical stimulation of the digital nerves of the left hallux Electrode 2 at vertex.

Spontaneous, Reflex and Action Myoclonus with Epilepsia Partialis Continua, Jacksonian and Grand Mal Seizures

Case 11. P.M. (Maudsley Hospital No. 823501), a 21-year-old man who developed left-sided focal epilepsy at the age of 9 yrs. He was the product of a normal full-term delivery, and there was no family history of neurological disease. His seizures always started in the left hand with a feeling like an electric shock in the lateral border of the hand. The fingers would then tingle and go rigid for a few seconds. Following this warning, he would lie down, his arm would shake and become flexed and abducted at the elbow, and his head turned to the left. These seizures often spread to involve the whole body, although he rarely lost consciousness. He has been treated with a large variety of antiepileptic drugs including phenytoin, carbamazepine, clonazepam, primidone and sodium valproate. Despite these different therapeutic measures, his epilepsy remained poorly controlled. He had three to four partial motor and focal seizures per week, resulting in dismissal from his job as a gardener.

The spontaneous jerks consisted mainly of continuous but arrythmic abduction of the left thumb, flexion of the first finger and extension of the middle finger. Light touch or pin-prick to the palmar or dorsal surfaces of the left hand, particularly to the pads of the thumb and fingers and to the adjacent surfaces of the back of the thumb and first finger, could provoke a synchronous jerk of the thumb and fingers. Tendon taps anywhere on the hand, but particularly to the forefinger or thumb, elicited similar jerks. Voluntary movements of the hand appeared to increase the size of the jerks, but had little effect on their frequency.

Two-point discrimination, light touch and pin-prick were reduced all over the left hand. Joint position sense also was diminished at the fingers and wrist. Motor power was normal, although he could not execute rapid alternating movements of the wrist or fine finger movements. Tendon jerks were normal as were the cranial nerves. The rest of the neurological and physical examination was normal. EEG studies (Dr M. Driver) revealed a complex, generalized mixture of pathological changes. A 3 to 5 Hz rhythm was recorded bilaterally with frontal predominance, and tended to be slower over the right hemisphere. This was interrupted by semirhythmic repetitive spikes over the left and right central regions. A CT scan showed mild right cortical atrophy particularly over the central and parietal regions. Serum immunoglobulin and viral studies, and repeated CSF examinations were normal. No definite clinical diagnosis was reached. Because of the severity and poor control of his epileptic seizures he was referred for neurosurgery (Mr C. Polkey). During the operation electrocorticography allowed identification of an abnormally functioning area of parietal cortex. This portion was excised, resulting in abolition of the left hand myoclonus. The pathological analysis of the biopsy was inconclusive. There was no evidence of chronic encephalitis.

Physiological studies. The results of physiological and anatomical investigation in this patient are to be the subject of a future detailed publication, so only a summary of the findings will be presented here.

The EMG correlate of the spontaneous muscle jerks was a 20 to 30 ms burst activity, synchronous in first dorsal interosseous, hypothenar, thenar and forearm muscles.

Electrical stimulation of the digital nerves of the forefinger with ring electrodes provoked a reflex muscle jerk, with a latency to onset of the EMG activity of 50 ms (in first dorsal interosseous). This was frequently followed by a smaller burst of activity some 50 ms later. The same electrical stimulus also evoked a large contralateral SEP over the sensorimotor cortex with a latency to the peak of P1 of 30 ms, and amplitude of P1-N2 of 45 μV. Cervical SEPs and the N1 component of the cortical SEP were of normal amplitude and latency. Back-averaging the EEG preceding spontaneous myoclonic jerks in the first dorsal interosseus muscle revealed a positive-negative wave over the contralateral somatomotor cortex. The positive peak occurred some 20 ms before the onset of the EMG jerk.

DISCUSSION

All the patients described appear to have myclonus as a result of abnormal electrical discharges arising in the cerebral cortex. The main purpose of this paper is to illustrate the range of clinical features that such discharges can provoke. These extend from isolated spontaneous action or stimulus-sensitive myoclonus, with different patients responding to different stimuli, through to epilepsia partialis continua and frank motor or generalized epilepsy. We have chosen patients to illustrate the subtle gradations between these extremes.

The clinical presentation of the myoclonus in these patients varied through pure cutaneous reflex myoclonus (Case 1); pure stretch myoclonus (Case 2); pure action myoclonus (Case 4); combined cutaneous, stretch and visual reflex myoclonus (Case 3); combined action and cutaneous reflex myoclonus (Case 5); combined action, cutaneous and stretch reflex myoclonus (Case 6); combined action, cutaneous and visual reflex myoclonus (Case 7); combined spontaneous, action, cutaneous and stretch reflex myoclonus (Case 8); combined, cutaneous and stretch reflex myoclonus (Case 10) and combined spontaneous, action, cutaneous and stretch reflex myoclonus (Cases 9 and 1). Cases 4, 7, 8, 9, 10 and 11 had grand mal epilepsy. This was mild and infrequent in Cases 7 and 11. Cases 10 and 11 also had typical focal motor Jacksonian seizures. Cases 9, 10 and 11 clinically were considered also to exhibit epilepsia partialis continua which requires further comment.

It is difficult to define epilepsia partialis continua. Juul-Jensen and Denny-Brown (1966) introduced their review of this topic by stating 'By EPC we mean chronic muscular twitching repeated at fairly regular short intervals in one part of the body for a period of days or weeks'. By this definition, Case 6 also would be considered by many as exhibiting epilepsia partialis continua. However, it was possible to show that this patient's myoclonus could be abolished by complete relaxation of the right arm, so that in fact his myoclonus was precipitated by action or somaesthetic stimuli. We take the view that a critical additional feature of epilepsia partialis continua is that it should occur *spontaneously*. In many patients with this condition, for example the majority of those described by Thomas *et al.* (1977), epilepsia partialis continua appeared to occur only spontaneously. However, a few of their patients noted that action aggravated the jerks, and we have shown that both action and a variety of somaesthetic stimuli clearly provoke jerks in some patients. Accordingly, we would revise the definition of epilepsia partialis continua to be 'spontaneous regular or irregular clonic muscle twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for a period of hours, days or weeks'.

Despite the various clinical manifestations exhibited by our patients all seemed to have a disorder of their cerebral cortex. We attribute their myoclonus to electrical discharges arising in the sensorimotor cortex because either they had an abnormal cortical potential preceding spontaneous or action-induced jerks, or because sensory stimuli evoked giant cortical potentials preceding their reflexly-evoked myoclonic jerks. In either case, the cortical potentials were localized to, or were maximal over, the contralateral sensorimotor cortical region. The shape of the cortical potential preceding spontaneous or action-induced jerks was similar to that of the P1-N2 component of the SEP, as has been noted previously by Shibasaki *et al.* (1978), and Rothwell *et al.* (1984). However, this does not necessarily mean that they arise from the same source.

The interval between the positive peak of the cortical potential and the onset of spontaneous or reflex myoclonus was of the order of 20 ms in the arm. This is consistent with rapid conduction down a direct corticospinal pathway (Pagni *et al.*, 1964; Merton and Morton, 1980; Merton *et al.*, 1982), and is compatible with involvement of motor cortex and pyramidal tract mechanisms in the myoclonus. Thus the myoclonus that we have studied appears to utilize direct cortico-motoneuron pathways and, indeed, was termed 'pyramidal myoclonus' by Halliday (1967). However, we cannot exclude, on the evidence available, additional involvement of extrapyramidal pathways.

At first sight, the cortical potentials preceding spontaneous or action-induced jerks, and the giant SEPs, might be considered to represent an abnormal synchronous discharge of motor cortical output neurons. However, elsewhere (Rothwell *et al.*, 1984) we have drawn attention to evidence against this hypothesis. Thus certain drugs such as lisuride and clonazepam can reduce or abolish the reflexly-evoked myoclonus, but have no effect or even increase the size of the SEPs. In addition, the source of the abnormal SEPs may not correspond accurately to the motor cortex, but often appears to lie posterior to the central sulcus. This was proven to be the case with electrocorticography in Case 11. As far as reflexly-evoked cortical myoclonus is concerned, we must conclude that the giant SEPs associated with the jerks, particularly their P1-N2 component, are not necessarily arising in motor cortex. Whether this also is true for the similar potentials preceding spontaneous or action-induced jerks is not certain. Nor is it clear that the potentials evoked by cutaneous or stretch stimuli are arising from the same source. More detailed study of the exact location of the sources of the potentials preceding spontaneous and action-induced myoclonus, and of those evoked by different sensory stimuli, is required to explore these points.

The exact site of the abnormal cortical potentials has implications for defining the details of the abnormality responsible for cortical myoclonus. Thus, in patients with abnormal SEPs localized posterior to the central sulcus, it may be that the motor cortex itself is normal, but that it is driven by an abnormal input from sensory cortex. Indeed, a range of abnormalities of sensorimotor cortical function can be conceived as causing different types of cortical myoclonus. Thus it could arise from abnormal sensory input to sensory (or motor) cortex, from abnormal processing of normal sensory input in sensory cortex leading to disordered sensorimotor cortical drive, from spontaneous sensory cortical discharges, from abnormal processing of normal inputs from sensory cortex into motor cortex, or from spontaneous discharges of motor cortical output neurons. Deafferented neocortex exhibits a tendency to paroxysmal discharges, perhaps as a result of supersensitivity of postsynaptic receptors (Halpern, 1972) associated with loss of dendritic spines (Ward, 1969). We believe that the spectrum of types of cortical myoclonus (and sometimes motor and generalized epilepsy) described in our patients may represent variations on these themes. However, we can provide little evidence from our data to dissect out the exact mechanism involved in individual patients. In Case 11, the results of PET scanning and electrocorticography strongly suggested that the primary abnormality in this patient lay in the sensory cortex. The size of the N1 component of the SEP, which represents the arrival of the afferent volley in the sensory cortex, was normal in all cases, so it appears that none of our patients had grossly abnormal sensory input into cortex. However, Jones (1982) has reported a single patient in which this appeared to be the case. Our Case 10 may have had a primary abnormality of the motor cortex, for he exhibited only focal spontaneous and action-induced myoclonus. A primary motor cortical abnormality probably was the cause of the myoclonus in the patient described by Kugelberg and Widén (1954). We cannot comment further on the detailed pathophysiology of the myoclonus in our other patients, but we must consider the equally vexing problem of the pathology causing their illnesses.

It is remarkable that we are uncertain of the pathology and aetiology of many of the cases described here. Thus, the cause of illness in Cases 6, 9, 10 and 11 is unknown. Even in Case 11 in whom a cortical resection was undertaken with subsequent histology, the pathology was indeterminate, as was the case in Kugelberg and Widén's patient (1954). It may be that studies of detailed cortical cytoarchitectonics and fibre connections will be required to decipher the problem, and these are not yet part of the routine neuropathological procedure.

Equally remarkable is that in the remaining patients (Cases 1, 2, 3, 4, 5, 7 and 8), the main pathology, based upon clinical and CT findings, was of cerebellar damage. This also was true in the patient of Carmichael (1947) studied in life by Dawson (1947) and pathologically by Greenfield (*see* Marsden *et al.*, 1973). Indeed, this was true of another patient with dyssynergia cerebellaris myoclonica described by Marsden *et al.* (1973), study of whom led us to conclude that 'in certain patients with myoclonus epilepsy, of the variety in which jerks can be evoked by sensory stimuli, these myoclonic jerks are, really, deranged cortical stretch reflexes' (Marsden *et al.*, 1973). This patient also has come to necropsy, but no relevant abnormality of the brain was found on routine neuropathology (Dr I. Janota). The presence of a cerebellar syndrome in so many of these patients hints at the possibility that their myoclonus was due to abnormal cerebellar input into, perhaps, a normal sensorimotor cortex. Refined neuropathology of such cases in the future will be necessary to solve this problem.

Cortical reflex myoclonus is of particular interest, for it shows that afferent input, from a variety of sources, may trigger myoclonic jerks, epilepsia partialis continua, and even Jacksonian seizures. It is now known that afferent information from skin joints and muscles (*see* Friedman and Jones, 1981) project to the sensorimotor cortex. In view of this anatomical and physiological evidence for projection of many peripheral somatic afferent inputs to sensorimotor cortex, it is not perhaps surprising that there is a wide variety of clinical types of cortical reflex myoclonus, differing in their necessary provocative stimuli, and in their association with other epileptic phenomena.

The spectrum of clinical features presented by the patients selected for description in this paper raises the important question of the relation of myoclonus to epilepsy. Our conclusion is that cortical reflex myoclonus, spontaneous cortical myoclonic jerks, epilepsia partialis continua, and Jacksonian motor seizures, with or without secondary generalization, form a continuum of epileptic activity centred on the sensorimotor cortex. The interictal surface spike discharge in epilepsy respresents a deeper cortical paroxysmal depolarization shift in epileptic neurons (Ward, 1969; Prince, 1978). In experimental epilepsy induced, for example, by local application of penicillin to the motor cortex, the positive wave recorded from the surface of the brain coincides with a negative field potential in lamina V of the motor cortex, indicating the depolarization of large output neurons in this cortical layer (Elger *et al.*, 1981). Negative field potentials in lamina V are associated with spinal field potentials, indicating that they generate a descending volley which eventually excites spinal motoneurons to cause a myoclonic jerk. The positive potential preceding the myoclonic jerks recorded in our patients, either in response to peripheral stimuli, or occurring spontaneously and detected by back-averaging, may represent a paroxysmal depolarization shift in lamina V sensorimotor cortical neurons. If in sensory cortex, this may drive motor cortex to cause myoclonic jerks. If in motor cortex, this may directly produce myoclonic jerks.

Of considerable interest is the observation that local negative field potentials produced by injection of penicillin into lamina V of the motor cortex of the rat may be associated with only very small positive potentials recorded at the cortical surface (Elger and Speckmann, 1980; Elgar *et al.*, 1981). This raises the possibility that the distant EEG recorded *via* scalp electrodes in man may not detect localized events in lamina V of the sensorimotor cortex. There may therefore be patients in whom cortical myoclonus may occur without EEG correlates, even with back-averaging techniques.

The spectrum of cortical myoclonus may be conceived as follows (fig. 9). Some patients may have unstable sensorimotor cortical responses to a variety of somatic afferent inputs, from skin, joints or muscle, and so exhibit cortical reflex myoclonus. Many of these patients also exhibit unstable responses to those signals responsible for driving the sensorimotor cortex to produce willed movement, so causing action myoclonus. Such signals associated with voluntary movement may be those arriving at the sensorimotor cortex from other cortical areas, the basal ganglia, or the

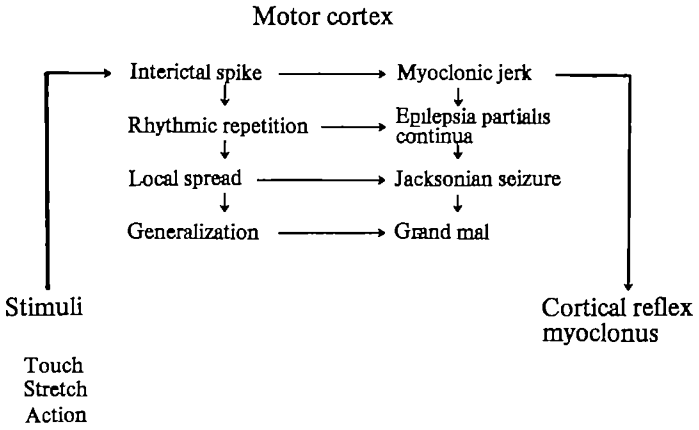


FIG. 9. Summary of relationships between cortical myoclonus and epilepsy (*after* Marsden, 1980) These events may occur in the motor cortex, as labelled, but, as emphasized in the text, there may be patients in whom motor cortical mechanisms are normal. In these cases, the motor strip may be driven to discharge and produce myoclonic jerks by an abnormal input from other areas of the brain.

cerebellum. In addition, spindle discharge that accompanies willed human muscle contraction (Vallbo, 1974) could trigger such sensorimotor cortical discharge to cause myoclonic jerks. Other patients may have spontaneous discharges of sensorimotor cortical neurons, to cause spontaneous myoclonic jerks, with or without afferent triggers. In other patients the sensorimotor cortical neurons may discharge spontaneously and repetitively, with or without afferent triggers, to produce epilepsia partialis continua. If such discharges spread within the sensorimotor cortex, Jacksonian motor seizures then occur, with or without secondary generalization. Viewed in this light, cortical myoclonus, whether reflex or spontaneous, is a part of the spectrum of epilepsy, as illustrated by some of the patients described here who have all manifestations of this spectrum.

Such epileptic phenomena are not confined to cerebral cortex. Myoclonus may arise in the brainstem in experimental animals (Zuckermann and Glaser, 1972) or man (reticular reflex myoclonus) (Hallett *et al.*, 1977), or from the spinal cord (segmental or spinal myoclonus) (Halliday, 1967), where again it may be triggered by afferent input (Davis *et al.*, 1981).

ACKNOWLEDGEMENTS

We should like to thank all the patients mentioned in this study for their willingness to participate in the electrophysiological testing. This work was supported by the Medical Research Council of Great Britain. J.C.R. is a Royal Society University Research Fellow.

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(*Received May 15, 1984. Revised August 20, 1984. Accepted August 31, 1984*)

Brain (1985), **108**, 225–240

PATHOGENESIS OF GIANT SOMATOSENSORY EVOKED POTENTIALS IN PROGRESSIVE MYOCLONIC EPILEPSY

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SUMMARY

Fifty-seven consecutive patients with myoclonus from various causes were studied by electrophysiological techniques. Giant somatosensory evoked potentials (SEPs) were observed almost exclusively in patients with progressive myoclonic epilepsy (PME) and diseases with similar clinical features that included lipidosis, neuronal ceroid lipofuscinosis and posthypoxic myoclonus. On the basis of combinations of the giant SEP and the myoclonus-related cortical spike demonstrated by jerk-locked averaging, myoclonus in these patients was classified into four types. In patients with 'cortical reflex' myoclonus (type I) who showed both the giant SEP and the myoclonus-related cortical spike, these two cortical activities were similar in terms of wave form, scalp topography, time relationship to either the long latency (C) reflex or myoclonus, the following cortical excitability, the effect of antimyoclonus drugs and alterations during slow wave sleep. It is therefore postulated that the giant SEP is generated, at least in part, by common physiological mechanisms to the myoclonus-related cortical spike, or that the latter may comprise a constituent of the former. In most patients with PME or allied diseases, both afferent and efferent components of the SEP are enhanced, but in some patients, only one of the two components seems to be predominantly enhanced.

INTRODUCTION

Since Dawson (1946, 1947) found an extremely large somatosensory evoked potential (SEP) in a patient with myoclonic epilepsy, the giant SEP has been studied by many investigators (Watson and Denny-Brown, 1955; Halliday, 1967; Halliday and Halliday, 1970; Pagni *et al.*, 1971; Sutton and Mayer, 1974; Halliday, 1975; Sutton, 1975; Chadwick *et al.*, 1977; Engel *et al.*, 1977; Rosén *et al.*, 1977; Shibasaki *et al.*, 1978; Hallett *et al.*, 1979; Franceschetti *et al.*, 1980; Kelly *et al.*, 1981). The giant SEP was shown to be characteristic of 'pyramidal' myoclonus by Halliday (1967) and of 'cortical reflex' myoclonus by Chadwick *et al.* (1977) and Hallett *et al.* (1979). Shibasaki *et al.* (1978) reported that, in cases of 'cortical reflex' myoclonus,

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the $\overline{N33}$ component of the giant SEP was similar to the cortical spike, which was demonstrated to be time-locked to the spontaneous myoclonus by jerk-locked averaging (Shibasaki and Kuroiwa, 1975; Chadwick *et al.*, 1977), in its waveform, time relationship and scalp topography, and proposed an involvement of similar physiological mechanisms in the genesis of both cortical activities. Hallett *et al.* (1979) also proposed a common mechanism for the giant SEP and the jerk-locked cortical spike. This paper will report further evidence to support this hypothesis, and discuss the pathogenesis of the giant SEP.

SUBJECTS

The subjects comprised 57 patients, 29 males and 28 females, who presented with various kinds of myoclonus. Most of the 30 patients previously studied by Shibasaki *et al.* (1978) were reexamined and are included in the present series. Their ages ranged from 8 to 73 years. The diagnostic classification and numbers of cases in each disease category are shown in Table 1.

Nineteen patients had convulsive seizures, which constantly began with myoclonic jerks. They also showed myoclonus of mainly postural and action type. The underlying cause was undetermined and these patients were diagnosed as progressive myclonic epilepsy (PME). Seven of them showed cerebellar ataxia in addition to action myoclonus, and their family history suggested autosomal recessive inheritance. They may represent the Ramsay Hunt syndrome. All 4 patients with lipidosis had retinal cherry-red spots, action myoclonus, cerebellar ataxia and generalized convulsive seizures. Three of them showed a gargoyle-like appearance and were demonstrated to have a deficiency of both sialidase and β-galactosidase. Another patient with lipidosis, without gargoylism, had a deficiency of sialidase alone. The diagnosis of Lafora body disease and neuronal ceroid lipofuscinosis was confirmed by biopsy of liver and rectal mucosa, respectively. A patient with the opsoclonus-polymyoclonia syndrome was considered to have acute cerebellitis, and recovered well. A diagnosis of Creutzfeldt-Jakob disease (CJD) was confirmed by post-mortem examination in 2 patients and made clinically in 1. Nine patients with 'epilepsy with myoclonus' had generalized convulsive seizures

TABLE 1 DIAGNOSTIC CLASSIFICATION OF THE SUBJECTS

	Cases
Progressive myoclonic epilepsy	19
Cherry-red spot-myoclonus syndrome	4
Sialidase and β-galactosidase deficiency	3
Sialidase deficiency	1
Lafora body disease	1
Neuronal ceroid lipofuscinosis	1
Posthypoxic myoclonus	2
Opsoclonus-polymyoclonia syndrome	1
Creutzfeldt-Jakob disease	3
Epilepsy with myoclonus	9
Essential myoclonus	5
Oculo-palatal-somatic myoclonus	2
Spinal myoclonus	2
Others	8
Total	57

and intermittent nonprogressive myoclonus. Essential myoclonus was defined as nonprogressive myoclonus without associated convulsive seizures, mental impairment or other neurological deficits. Two patients with oculopalatal-somatic myoclonus had brainstem lesions, probably haemangiomata. Eight patients with other diseases consisted of 2 with midbrain vascular lesions, 2 with encephalitis and 1 each with presenile dementia, spinocerebellar degeneration, Huntington's chorea and focal myoclonus of unknown aetiology.

In this paper, patients with PME, the cherry-red spot-myoclonus syndrome, Lafora body disease, ceroid lipofuscinosis and posthypoxic myoclonus are referred to as 'PME and allied diseases' since they showed common clinical manifestations, especially postural and/or action myoclonus. Generalized convulsive seizures occurred in 21 of the 27 patients with PME and allied diseases.

METHODS

Electrophysiological studies included an electroencephalogram (EEG)-electromyogram (EMG) polygraph, somatosensory evoked potentials (SEPs) combined with recording of long-latency reflexes, paired-stimulation SEPs in some patients, jerk-locked averaging, jerk-locked SEPs and, in some patients, studies of drug effects and SEPs during sleep. All studies were carried out in a dimly lit quiet room with the subject either supine or sitting.

An SEP was obtained by stimulating the median nerve at the wrist with electric shocks delivered at a rate of 1/s as a square wave pulse of 0.1 or 0.2 ms duration. The stimulus strength was adjusted to 10 per cent above the motor threshold. For recording, multiple cup electrodes were placed on the scalp, including C3, Cz and C4 positions (International 10–20 system). Electrode impedance was kept below 5 kΩ. All electrodes were referred to an ipsilateral ear electrode, and bipolar derivations were occasionally added. To record long-latency reflex or C reflexes (Sutton and Mayer, 1974), a pair of surface electrodes was placed on the thenar muscle of the stimulated side, and also on other muscles as necessary. Filter setting for EEG was usually 1 to 1000 Hz (−3 dB) and that for EMG was 15 to 1000 Hz (−3 dB). The EEGs and the rectified EMG were fed into a computer and averaged by using the stimulus pulse as a trigger. The number of sweeps averaged was 64 to 200. An SEP was judged as 'giant' when the component corresponding to $\overline{\text{P25}}$ of the normal SEP (terminology of Donchin *et al.* (1977)), measured as the amplitude difference from the $\overline{\text{N20}}$ peak at the contralateral central area, was larger than 8.6 μV, or that corresponding to $\overline{\text{N33}}$ measured from the $\overline{\text{P25}}$ peak was larger than 8.4 μV (Shibasaki *et al.*, 1977). Components of giant SEPs were identified by the corresponding component of normal SEPs (Shibasaki *et al.*, 1977).

In some patients, a pair of electric shocks was delivered to the median nerve at the wrist with an interstimulus interval (ISI) of 5 to 100 ms, and an SEP was obtained by the same method as used for the single stimulus SEP. The first stimulus pulse was used as a trigger for averaging.

EEG correlates of 'spontaneous' myoclonus were studied by the conventional EEG-EMG polygraph and by jerk-locked averaging (Shibasaki and Kuroiwa, 1975; Chadwick *et al.*, 1977). The EMG was recorded by a pair of surface electrodes placed 3 cm apart on muscles showing frequent myoclonus. The filter setting was 15 to 1000 Hz (=3 dB). The myoclonic EMG discharge was rectified and a pulse was obtained when the rectified EMG reached a preset level. EEGs, recorded by using the same electrode placement as used for the SEP, and the rectified EMG were averaged with a backward averaging program, using the EMG onset pulse as a trigger. Window time and number of sweeps varied depending on the kind of myoclonus and purpose of each study. In a patient with PME, scalp topography of the $\overline{\text{P25}}$ component of giant SEP and that of the myoclonus-related cortical spike were drawn by a computerized mapping program.

To record jerk-locked SEPs, an electric shock was delivered to the median nerve at the wrist at precisely the time of or at varying intervals after the onset of the rectified myoclonic EMG discharge recorded from the corresponding upper limb muscle. EEGs and rectified EMG were then averaged with the backward averaging program by using the EMG pulse as a trigger. A cortical excitability curve after myoclonus was obtained by comparing the amplitude of the $\overline{\mathrm{P25}}$ or $\overline{\mathrm{N33}}$ component of the SEP thus recorded with that of the SEP recorded irrespective of myoclonus in the same subject.

In some patients with PME, SEP and jerk-locked averaging were recorded before and after the antimyoclonus medication including clonazepam and 5-hydroxytryptophan. In 4 patients with PME, the SEP was studied during different stages of spontaneous nocturnal sleep.

Measurements were made by computer cursoring. The amplitude of an averaged EEG potential was measured from the preceding peak of the opposite polarity to that peak, as well as from the visually determined baseline to the peak. Data were written out on an X-Y plotter.

RESULTS

Occurrence of Giant SEPs and Long-latency (C) Reflexes

Giant SEPs were seen in 23 of the 27 patients with PME and allied diseases (cherry-red spot-myoclonus syndrome, Lafora body disease, ceroid lipofuscinosis, and posthypoxic myoclonus) studied, but only in 1 (with CJD) among 23 patients belonging to other disease categories (Table 2). An enhanced C reflex was seen in 21 out of 25 patients with PME and allied diseases studied, but only in 1 among 7 other patients (Table 2). All 21 patients in the former group who showed an enhanced C reflex had giant SEPs.

Characteristics of Giant SEPs and C reflexes

Giant SEPs seen in patients with PME and allied diseases were characterized by extremely large $\overline{\mathrm{P25}}$ and $\overline{\mathrm{N33}}$ components (fig. 1). The amplitude of the $\overline{\mathrm{P25}}$ and $\overline{\mathrm{N33}}$ components was as large as 34 μV and 63 μV as measured from the preceding peak of the opposite polarity, or as large as 30 μV and 42 μV as measured from the baseline, respectively. In contrast, the initial negative component, $\overline{\mathrm{N20}}$, was not

TABLE 2 INCIDENCE (NUMBER OF PATIENTS) OF GIANT SEPs AND LONG-LATENCY (C) REFLEXES BY CLINICAL DIAGNOSIS (*SEE* TABLE 1)

	Giant SEPs		*C reflex*	
	Studied	*Present*	*Studied*	*Present*
Progressive myoclonic epilepsy	19	17	17	15
Cherry-red spot-myoclonus syndrome	4	4	4	4
Lafora body disease	1	0	1	0
Ceroid lipofuscinosis	1	1	1	1
Posthypoxic myoclonus	2	1	2	1
Opsoclonus-polymyoclonia	1	0	1	0
CJD	3	1	1	0
Epilepsy with myoclonus	6	0	1	0
Essential myoclonus	5	0	1	0
Palatal myoclonus	1	0	0	0
Others	7	0	3	1
Total	50	24	32	22

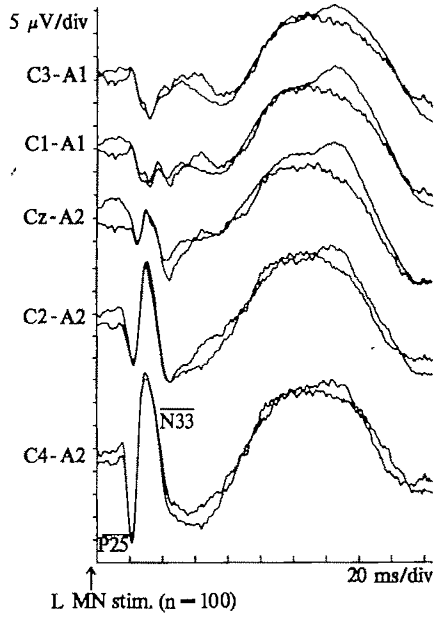


FIG. 1. SEPs following left median nerve (MN) stimulation in a 22-year-old woman with PME. Average of 100 responses. The high amplitude P25-N33 components are maximal at the right central (C2 and C4) electrodes, and 10 ms later similar potentials of smaller amplitude are seen at the left central (C3 and C1) electrodes. Upward deflection denotes negativity at grid 1 in this and all other figures.

enhanced. Its maximal amplitude in the patient group was 4.7 µV whereas the mean amplitude of N20 in the normal control was 2.8 µV with a standard deviation of 1.4 µV (Shibasaki *et al.*, 1977). The N62 component was frequently absent, whereas the N150 component was often enhanced.

The high amplitude P25-N33 components were maximal at the central area contralateral to the stimulation, and widely distributed over the scalp (fig. 2). An enhanced positive potential was also recognized at the central area ipsilateral to the stimulation at a peak latency 10 ms longer than that of the P25 peak on the contralateral hemisphere, although the former was much smaller than the latter (fig. 1). There was no gradual propagation of the peak latency from electrode to electrode within each hemisphere.

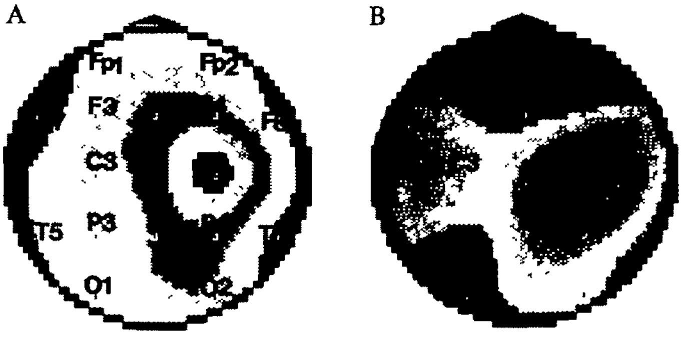


FIG. 2. Scalp topography of the P25 component of giant SEP (A) and of the initial positive component of the myoclonus-related cortical spike (B) in a 22-year-old man with PME. The left median nerve was stimulated for the SEP, and myoclonus was recorded from the left thenar muscles for jerk-locked averaging. Those two components are maximal at the contralateral central area, but the giant SEP component is more widely distributed than the myoclonus-related spike.

A C reflex was recognized in the thenar muscles of the stimulated side at a latency of 31 to 58 ms after stimulation or at a time interval of 11 to 24 ms after the $\overline{\text{P25}}$ peak of the giant SEP (fig. 3A). In some patients, a long-latency reflex was also recorded from the thenar muscles of the opposite (nonstimulated) hand, its onset latency being 10 ms longer than that of the C reflex of the stimulated side. In an 8-year-old patient with ceroid lipofuscinosis, both giant SEPs and long-latency reflexes were also recorded from foot muscles following tibial nerve stimulation at the ankle (fig. 3B). The time interval from the positive peak of the SEP to the long-latency reflex was 29.0 ms, whereas that from the $\overline{\text{P25}}$ peak of the median nerve SEP to the C reflex was 10.5 ms.

Six patients with PME and allied diseases showed double positive peaks of giant SEPs and double C reflexes (fig. 4). The latency difference between the two positive SEP peaks was approximately 25 ms and was very close to that between the two C reflexes (C1 and C2 in fig. 4). Thus the time interval from the first positive peak of the giant SEP to C1 was equal to that from the second positive peak of the giant SEP to C2.

Myoclonus-related Cortical Activity Studied by Jerk-locked Averaging

Among 17 patients with PME and allied diseases in whom the jerk-locked averaging technique was applicable, positive-negative, biphasic sharp EEG activity time-locked to the myoclonic jerks was demonstrated in 15. Five out of these 15 patients had no recognizable spikes in the routine EEG. In 12 patients, the myoclonus-related cortical spike was maximal at the central region contralateral to the myoclonus of an upper limb (figs. 2 and 5). It was maximal at the vertex when myoclonus was recorded from a lower limb (fig. 5). In 2 patients with PME showing

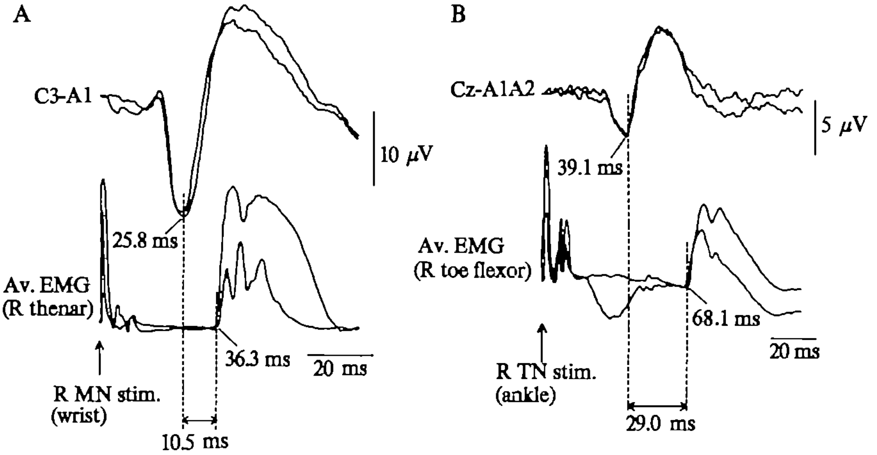


FIG. 3. Giant SEP and C reflex in response to right median nerve stimulation (R MN stim.) at wrist (A) and right tibial nerve stimulation (R TN stim.) at ankle (B) in an 8-year-old boy with neuronal ceroid lipofuscinosis. Average of 128 responses each.

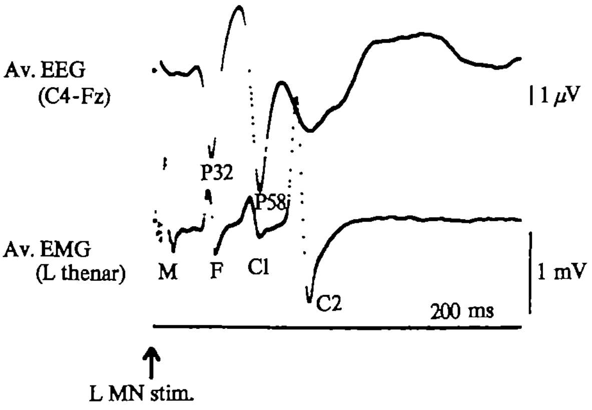


FIG 4. Double-positive peaks of giant SEP and double C reflexes in response to a single left median nerve stimulus (L MN stim) in a 22-year-old man with PME. Average of 64 responses. The latency difference between the two positive peaks of the SEP (P32-P58) is similar to that between the two C reflexes (C1-C2).

bilaterally synchronous myoclonus in proximal upper limb muscles, the myoclonus-related spike was maximal close to the vertex. The early positive peak of the myoclonus-related cortical spike preceded the onset of an upper limb myoclonic EMG discharge by 6 to 22 ms. The more proximal was the muscle from which the myoclonus was recorded, the shorter was the time interval, and *vice versa* (fig. 5).

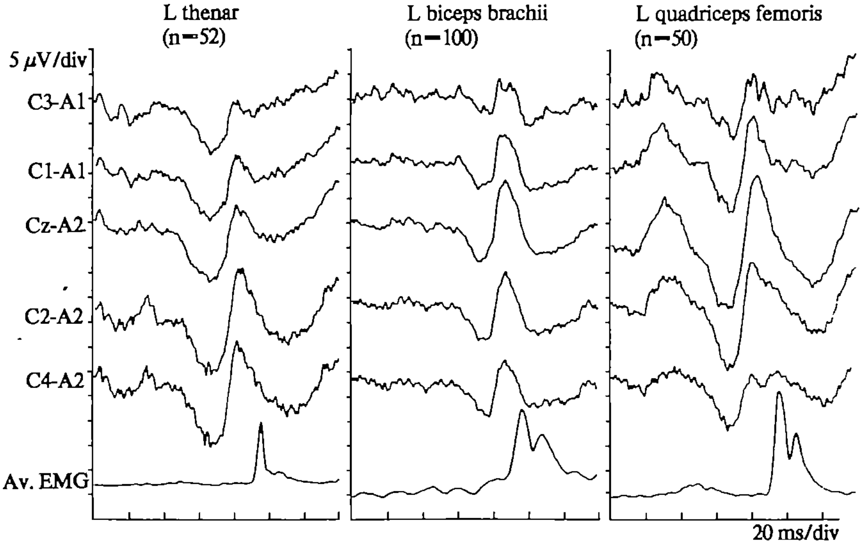


FIG 5 Myoclonus-related cortical spike demonstrated by jerk-locked averaging in a 22-year-old woman with PME. Av. EMG = averaged rectified EMG. Cortical spike time-locked to the myoclonus of the left thenar muscles, the left biceps brachii and the left quadriceps femoris is maximal at C2 and C4, Cz and C2 and Cz electrodes, respectively. The positive peak of the cortical spike precedes the onset of myoclonus of the left thenar muscles, the left biceps brachii and the left quadriceps femoris by 22 ms, 14 ms and 22 ms, respectively.

Among 13 patients classified into disease categories other than PME and allied diseases, 1 patient (with focal motor seizures) showed a myoclonus-related cortical spike, and 4 patients (3 with CJD) had a sharp negative wave in association with myoclonus.

Correlation between Giant SEPs and Myoclonus-related Cortical Spikes in Patients with PME and Allied Diseases

Thirteen patients with PME and allied diseases showed both giant SEPs and myoclonus-related cortical spikes (Table 3). In 1 patient (with ceroid lipofuscinosis), giant SEPs were present, but jerk-locked averaging did not demonstrate any cortical spikes. Six patients showed giant SEPs, but the jerk-locked averaging technique was inapplicable because of the infrequent occurrence of myoclonus. In 2 patients, jerk-locked averaging demonstrated myoclonus-related spikes, but the SEP was not enhanced. These 2 patients were those in whom myoclonus involved bilateral proximal muscles synchronously and the myoclonus-related spike was maximal near the vertex. In 1 patient (posthypoxic myoclonus), there were neither giant SEPs nor myoclonus-related cortical spikes, and in another patient (with Lafora body disease), giant SEPs were absent and myoclonus was too infrequent for jerk-locked averaging.

TABLE 3 INCIDENCE (NUMBER OF PATIENTS) OF GIANT SEPs AND MYOCLONUS-RELATED CORTICAL SPIKES DETECTED BY JERK-LOCKED AVERAGING IN PATIENTS WITH PROGRESSIVE MYOCLONIC EPILEPSY AND ALLIED DISEASES

Spike *Giant SEP*	*Present*	*Absent*	*Unable to test**	*Not tested*	*Total*
Present	13	1	6	3	23
Absent	2	1	1	0	4
Total	15	2	7	3	27

* Because of infrequent occurrence of myoclonus.

Comparison between Giant SEPs and Myoclonus-related Cortical Spikes in 'Cortical Reflex' Myoclonus

In 13 patients showing both giant SEPs and myoclonus-related cortical spikes, thus corresponding to 'cortical reflex' myoclonus (Chadwick *et al.*, 1977; Hallett *et al.*, 1979), both the $\overline{\mathrm{P25}}$-$\overline{\mathrm{N33}}$ components of giant SEPs and the myoclonus-related cortical spikes were positive-negative, biphasic potentials, although the former were usually larger than the latter. The scalp topography of these two activities was similar, although the $\overline{\mathrm{P25}}$-$\overline{\mathrm{N33}}$ components of giant SEPs were more widely distributed than the myoclonus-related spike (fig. 2). The time interval from the $\overline{\text{P25}}$ peak of the giant SEP to the onset of the C reflex was similar to or a little longer than that from the positive peak of the myoclonus-related cortical spike to the onset of myclonic jerk. Correlation between these two time intervals was impossible because myoclonus was recorded from various upper limb muscles whereas the C reflex was always recorded from the thenar muscles. In some patients in whom spontaneous myoclonic jerks were shown by jerk-locked averaging to spread from proximal to distal upper limb muscles, the long-latency reflexes showed exactly the same pattern of spread (fig. 6).

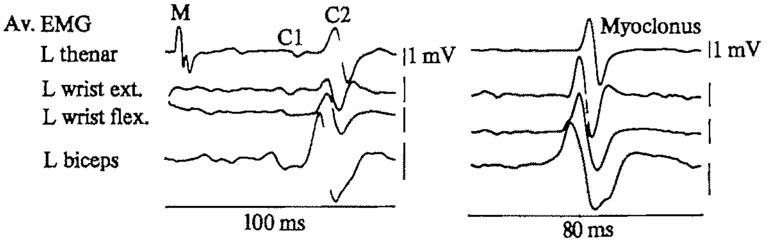


FIG. 6. Spread of spontaneous myoclonus and long-latency reflexes in a 22-year-old man with PME (the same patient as in fig. 4). With left median nerve stimulation (*left*, average of 64 responses), double long-latency reflexes (C1 and C2) are recognized, C2 being more prominent than C1. Spontaneous myoclonus from 4 different muscles was recorded by the jerk-locked averaging technique using the myoclonic discharge from the left thenar muscles as a trigger (*right*, average of 32 records) Both C1 and C2 show the same pattern of spread from proximal to distal muscles as the spontaneous myoclonus

In a patient with PME, results for jerk-locked SEPs were compared with those for paired stimulation SEPs (fig. 7). When the median nerve was stimulated at precisely the time of onset of myoclonus the $\overline{\text{P25}}$-$\overline{\text{N33}}$ components of the giant SEP recorded at the contralateral central electrodes were very prominent, were conducted to the ipsilateral hemisphere and were followed by an enhanced C reflex (fig. 7). When stimulated 35 ms after the onset of myoclonus, however, the $\overline{\text{P25}}$-$\overline{\text{N33}}$ components were smaller, conduction to the other hemisphere was much less prominent, and the C reflex was also smaller (fig. 7). Comparison of the $\overline{\text{N33}}$ amplitude of the myoclonus-locked SEP ($\overline{\text{N33}}$(JL-SEP)) with that of the SEP recorded irrespective of myoclonus ($\overline{\text{N33}}$(SEP)) revealed a relative enhancement of that component for 20 ms immediately after the onset of myoclonus, although it was slightly attenuated throughout the postmyoclonus period (fig. 8). Myoclonus in the left brachioradialis muscle was preceded by a cortical spike by 10.6 ms in this particular case (figs. 7 and 8).

For the paired stimulation SEPs, the giant SEP evoked by the second stimulus was more prominent with an ISI of 35 ms than one of 65 ms (fig. 7). A C reflex was

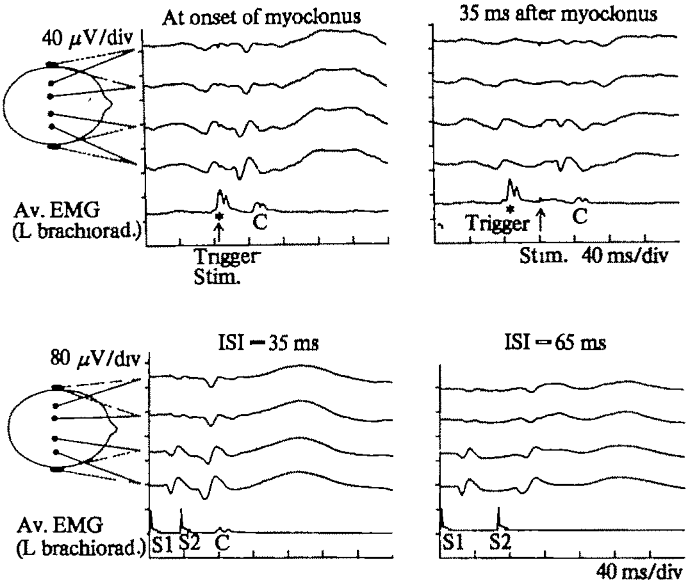


FIG. 7 Jerk-locked SEP and paired stimulation SEP in a 22-year-old woman with PME. In the jerk-locked SEP (*top*, average of 50 records), the giant SEP and C reflex are more prominent when stimulated at precisely the time of myoclonus than when stimulated 35 ms later. In the paired stimulation SEP (*bottom*, average of 100 responses), the giant SEP and C reflex are enhanced with an interstimulus interval (ISI) of 35 ms, but attenuated with that of 65 ms.

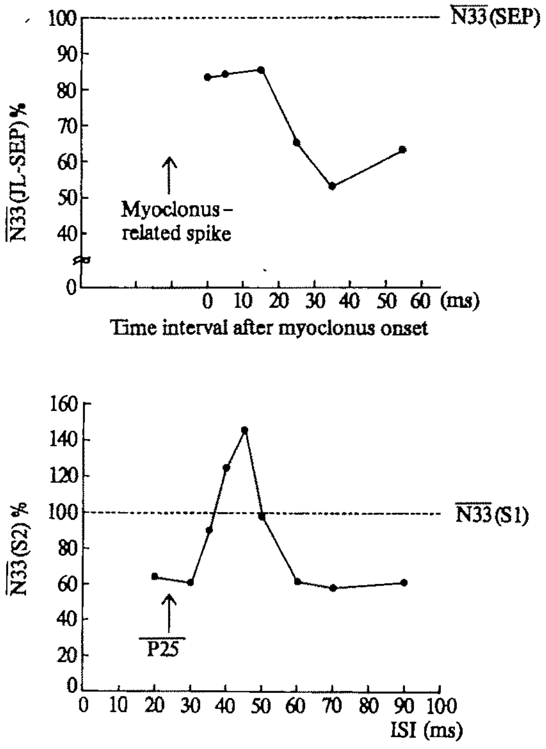


FIG. 8. Cortical excitability following the myoclonus-related cortical spike (*top*) and following the giant SEP (*bottom*) in a 22-year-old patient with PME (the same patient as in fig. 7). There is a relative enhancement of cortical excitability starting at about 10 ms after the positive peak of the myoclonus-related cortical spike as well as after the P25 peak of the giant SEP, and lasting for approximately 20 ms.

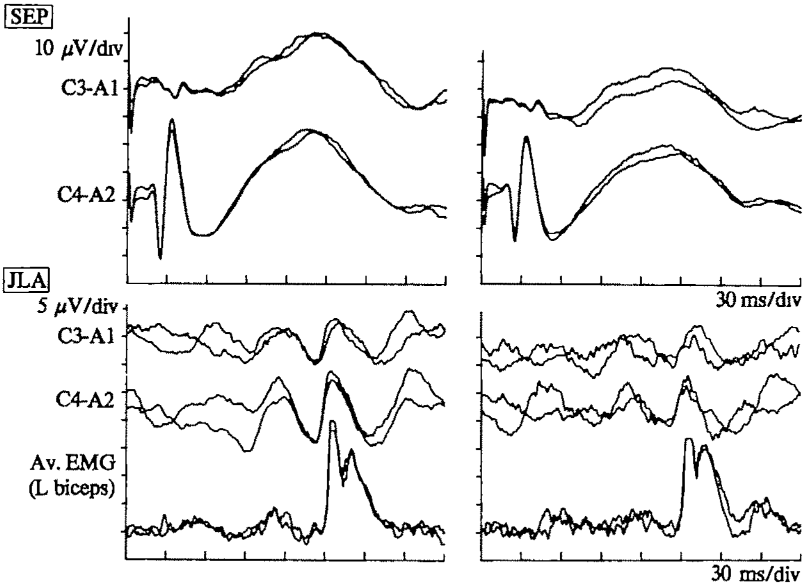


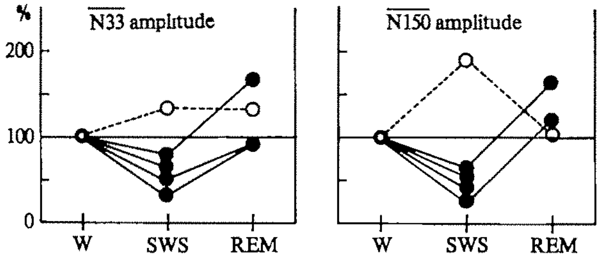
FIG. 9. Giant SEP and the myoclonus-related cortical spike before (*left*) and during (*right*) the i.v. infusion of 100 mg 5-hydroxytryptophan (5-HTP) in a 22-year-old woman with PME. The SEP was recorded in response to the left median nerve stimulation, and myoclonus was recorded from the left biceps brachii muscle for the jerk-locked averaging (JLA). Both the P25-N33 components of the giant SEP (*top*, average of 100 responses) and the myoclonus-related cortical spike (*bottom*, average of 50 records) are attenuated by the treatment.

recognized with an ISI of 35 ms, but not with one of 65 ms (fig. 7). There was an absolute enhancement of the N33 component starting 10 ms after the P25 peak of the first SEP and lasting for 20 ms (fig. 8).

An i.v. infusion of 100 mg 5-hydroxytryptophan in a patient with PME markedly reduced the incidence of both myoclonus and EEG spikes. The amplitude of the P25 and N33 components of the giant SEP decreased from 24.5 to 17.6 μV and from 47.5 to 34.0 μV respectively (fig. 9). The myoclonus-related cortical spike demonstrated by jerk-locked averaging also decreased in its amplitude from 11.8 to 6.4 μV (fig. 9). In another patient with PME, the i.v. administration of 10 mg diazepam or 250 mg diphenylhydantoin resulted in a decreased incidence of myoclonus and a significant reduction in SEP amplitude.

In all of 4 patients with PME who were studied during spontaneous sleep, myoclonus was markedly suppressed during slow-wave sleep. Giant SEPs were significantly attenuated during slow-wave sleep (fig. 10). In 2 patients who were studied during rapid eye movement sleep, the giant SEPs were similar to those during wakefulness in 1 patient and enhanced in the other (fig. 10).

FIG. 10. Giant SEP during sleep in 4 patients with PME Both the N33 and N150 components of the giant SEP are smaller during slow-wave sleep (SWS) than during wakefulness (W) in all 4 patients studied. REM = rapid eye movements. Patients (filled circle); control (open circle).



DISCUSSION

In the present study, the typical giant SEP was observed almost exclusively in patients with progressive myoclonic epilepsy (PME) and allied diseases that included the cherry-red spot-myoclonus syndrome, neuronal ceroid lipofuscinosis and posthypoxic myoclonus. On the basis of the results of both SEP recordings and jerk-locked averaging, myoclonus seen in these patients can be classified into four types (Table 4). The most common in the present series was type I, in which the SEP was extremely enhanced and myoclonus was preceded by a cortical spike. This type corresponds to the 'pyramidal' myoclonus of Halliday (1967) or 'cortical reflex' myoclonus of Hallett *et al.* (1979). Two patients in the present series belonged to type II, in which the myoclonus-related cortical spike was demonstrated by jerk-locked averaging, but the SEP was not enhanced. In type III, the SEP was enhanced, but myoclonus was not associated with cortical spikes or occurred so infrequently that the jerk-locked averaging technique was inapplicable. If we define type IV as myoclonus which is neither associated with giant SEPs nor with cortical spikes, only 2 patients with PME and allied diseases belonged to this category. In fact, one of them had myoclonus too infrequently to enable jerk-locked averaging to be undertaken.

In cases of 'cortical reflex' myoclonus (type I), the giant SEP was usually larger and more widely distributed on the scalp than the myoclonus-related cortical spike,

TABLE 4 CLASSIFICATION OF MYOCLONUS SEEN IN PATIENTS WITH PME AND ALLIED DISEASES BASED ON SEP AND JERK-LOCKED AVERAGING, AND THE TWO COMPONENTS HYPOTHESIS FOR GIANT SEPs

Type	*No. of patients*	*Giant SEPs*	*Myoclonus-related cortical spikes*	*Enhanced component*
I	13	Present	Present	Both afferent and efferent
II	2	Absent	Present	Efferent
III	7	Present	Absent or myoclonus infrequent	Afferent
IV	2	Absent	Absent or myoclonus infrequent	None

although their maximal scalp locations were similar. It is therefore conceivable that the giant SEP as recorded from the scalp electrode in type I cases might contain the myoclonus-related cortical spike as one of its components. It is further speculated that the giant SEP seen in this type of myoclonus might be composed of at least two components, namely, one reflecting a hyperexcitability of the afferent system of the sensorimotor cortex and the other reflecting that of the efferent system. In types II and III, either the efferent or the afferent system respectively might be selectively hyperexcitable. Type IV does not appear to be associated with hyperexcitability of any of those cortical systems, and might therefore correspond to the 'reticular reflex' myoclonus of Hallett *et al.* (1977), although the polygraphic technique required to prove it was not employed in the present study.

In relation to the above discussion, it is noteworthy that patients who apparently have the same disease with the same clinical manifestations can show different electrophysiological abnormalities. Although the underlying mechanisms causing those differences remain to be solved, it should be kept in mind that, with special reference to type III myoclonus, epileptic discharges in the deep cortical layer may have little surface cortical correlates, as shown by Elger *et al.* (1981). Furthermore, some cases of stimulus-sensitive myoclonus show stimulus-specificity. Muscle stretch is the most effective stimulus in most cases (Dawson, 1947; Marsden *et al.*, 1973; Rosén *et al.*, 1977), but some cases are sensitive to touch or pressure but not to muscle stretch (Sutton, 1975). Since we have studied responses only to electric shocks, cases of types II and IV myoclonus could have responded with giant SEPs if other kinds of stimuli were used.

The giant SEP seen in cases of PME and allied diseases is characterized by remarkably enhanced components corresponding to $\overline{\mathrm{P25}}$ and $\overline{\mathrm{N33}}$ of the normal SEP, but the component corresponding to the initial negative potential $\overline{\mathrm{N20}}$ is not enhanced. Similar findings were reported by Rothwell *et al.* (1984). These observations seem to be significant in terms of the generator source of $\overline{\mathrm{N20}}$. If only the postsynaptic cortical potentials are enhanced in such cases, the present findings are in conformity with the current theory that attributes the generator source of $\overline{\mathrm{N20}}$ to the thalamocortical projection pathway or presynaptic cortical potentials (Kimura and Yamada, 1982; Maccabee *et al.*, 1983; Yamada *et al.*, 1984).

Shibasaki *et al.* (1978) and Hallett *et al.* (1979) proposed a common physiological mechanism in the genesis of the giant SEP and the myoclonus-related cortical spike in cases of 'cortical reflex' myoclonus. That hypothesis was based on the demonstration of a close similarity between the two cortical activities in terms of waveform, scalp topography, and temporal relationship to long-latency reflexes and spontaneous myoclonus, respectively (Shibasaki *et al.*, 1978). The present results, based on a larger number of patients, not only confirm these previous findings, but also provide additional evidence to support the hypothesis.

In a patient with PME, a relatively enhanced cortical excitability of 20 ms duration was demonstrated immediately after the onset of spontaneous myoclonus.

Since that myoclonus was preceded by a cortical spike by 10.6 ms, the enhancement of cortical excitability actually started at the latest 10.6 ms after the myoclonus-related cortical spike. Paired stimulation SEPs in the same patient demonstrated a similar enhancement of cortical excitability starting at 10 ms after the $\overline{\mathrm{P25}}$ peak of the giant SEP and lasting 20 ms. In both the jerk-locked SEP and paired stimulation SEP paradigms compared in the present study, we demonstrated a prominent extension of the giant SEP to the opposite hemisphere and a clearly enhanced C reflex during the short period of an enhanced cortical excitability. These findings suggest that there is a similar enhancement of cortical excitability after the myoclonus-related cortical spike and after the giant SEP.

With regard to a change in cortical excitability following electrical stimulation of peripheral nerve, Dawson (1947) reported, by a paired stimulation SEP technique in a patient with stimulus-sensitive myoclonus, its depression with ISIs of 10 to 30 ms and an enhancement with intervals from 60 to 100 ms, followed by another depression. Results reported by Sutton and Mayer (1974) in their patient with focal reflex myoclonus were similar to those in our present patient. They found a mild enhancement of cortical excitability with ISIs from 32 to 63 ms and also from 130 to at least 250 ms.

Rothwell *et al.* (1984) studied the effects of lisuride and clonazepam in 4 patients with PME and found no change in or even an increase of giant SEPs in spite of a reduction of spontaneous myoclonus and reflex muscle jerking. In contrast with their finding, an i.v. injection of 5-hydroxytryptophan in our patient with PME reduced myoclonic jerks, this being associated with a reduced amplitude of both the myclonus-related cortical spike and the giant SEP. Similar effects of anticonvulsants were observed in another patient. During slow-wave sleep studied in 4 patients with PME and allied diseases, giant SEPs as well as myoclonic jerks were remarkably suppressed. In addition, the enhanced long-latency (C) reflex (Sutton and Mayer, 1974) to electrical stimulation of peripheral nerve showed exactly the same pattern of spread from proximal to distal muscles as did spontaneous myoclonus, suggesting an involvement of similar physiological mechanisms in the genesis of both activities in the peripheral muscle.

These findings are in conformity with the hypothesis that the giant SEP frequently seen in patients with PME and allied diseases is generated, at least in part, by common physiological mechanisms to the myoclonus-related cortical spike, or that the former contains the latter as one of its constituents. Apparently spontaneous myoclonic jerks in patients with 'cortical reflex' myoclonus (type I) are therefore most likely to represent enhanced long-latency (C) reflexes in response to unnoticed stimuli, although the possibility of spontaneous discharges in the sensorimotor cortex causing spontaneous myoclonus cannot be entirely excluded.

Giant SEPs and enhanced C reflexes were not observed in patients with epilepsy with myoclonus, essential myoclonus, palatal myoclonus or the opsoclonus-polymyoclonia syndrome, suggesting that these conditions are not associated with cortical hyperexcitability. As indicated by Halliday and Halliday (1970), the demonstration of giant SEPs in the study of myoclonus patients is diagnostically significant. Patients with CJD usually manifest periodic myoclonus at rest which is accompanied by a cortical sharp wave corresponding to the periodic synchronous discharge (Shibasaki *et al.*, 1981), but they can show also 'cortical reflex' myoclonus during their clinical course.

ADDENDUM

The technique of jerk-locked SEP averaging and parts of figs. 7 and 8 are reported in more detail in *Neurology, Cleveland* (in press).

ACKNOWLEDGEMENTS

The authors are very grateful to Dr A. M. Halliday, the National Hospital for Nervous Diseases, Queen Square, London, for his valuable comments on and revision of this paper.

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(Received April 10, 1984. Revised August 20, 1984. Accepted September 4, 1984)

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CHRONIC OPTIC NERVE COMPRESSION

AN EXPERIMENTAL STUDY

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SUMMARY

Chronic progressive compression of the optic nerve in the cat was produced by an inflatable silicon rubber balloon implanted in the orbit. Within the first week the predominant pathological change was demyelination. Both partially and completely demyelinated fibres were seen at all stages of the experiments but by the fifth week some axons had been remyelinated by oligodendrocytes despite the continued presence of the balloon. The myelin sheaths of the new internodes were abnormally thin and short, and many showed an atypical paranodal organization. There was evidence of breakdown of some of the new internodes. The pathophysiology of optic nerve compression in man is reviewed.

INTRODUCTION

> It is true that while the optic nerve was in its state of extension, the sight was impaired; but, after seven years extension, how it came to recover itself in a month's time, without any alteration in the sight, but for the better, I leave to the speculation of the curious. Hope (1744)

The pathological basis for reversible visual loss due to tumours involving the visual pathways is poorly understood. Although there is a large literature on the histology of such tumours, little has been written on the changes they produce in the nerve fibres upon the integrity of which visual function ultimately depends. Lindenberg *et al.* (1973) described atrophy and gliosis in advanced cases but nothing is known of the histological changes in nerves from patients who have made a good recovery following removal of the tumour.

More is known about the effects of mechanical damage in the peripheral nervous system (Denny-Brown and Brenner, 1944*a*, *b*; Denny-Brown and Doherty, 1945; Aguayo *et al.*, 1971; Ochoa *et al.*, 1972; Ochoa and Marotte, 1973; Gilliatt, 1981), but because of differences in structure and organization in central tracts (Bunge, 1968; Peters *et al.*, 1976) and the limited capacity for functionally effective regeneration of the CNS (Ramón y Cajal, 1928; Berry, 1979) conclusions drawn from the study of peripheral nerve are of limited use in explaining the effects of central damage. We have therefore developed an experimental model of an expanding orbital mass.

When in clinical practice a mass impinges on neural structures the general term ‘compression’ is used without prejudice as to whether the tissue damage that results is caused by local pressure gradients, changes in length or other mechanical distortions. We use 'compression' in this sense in our paper. A preliminary account of some of this work has been published (Clifford-Jones *et al.*, 1980).

METHODS

Twenty-two cats (weights 2.2–4.5 kg) were used in the study. In 17 animals the orbital part of one optic nerve was compressed by an implant designed to simulate an expanding orbital tumour; 5 cats were used as controls. Six optic nerves from 3 cats killed after physiological experiments not involving the visual system were examined to provide normal data.

The Implant (fig. 1)

Each implant consisted of a polypropylene male adaptor plug (Abotts Laboratories) connected by thin silicon rubber tubing (Esco Rubber Ltd) to an inflatable balloon made of silicon rubber sheeting (Dow Corning). The plug was fitted with a self-sealing latex bung through which fluid could be injected. The plug and tubing were rigid compared with the sheeting and any increase in the volume of fluid within the implant resulted in an increase in size of the balloon which could be maintained for long periods. The length of the implant was 30 cm and the maximum capacity of the balloon was 2 ml, with a diameter of 1.5 cm when fully inflated.

Placement of Implant

Anaesthesia was induced and maintained with Saffan (Glaxo). The reservoir of the implant was placed under the skin through a small midline dorsal incision. The uninflated balloon end of the implant was pulled through a subcutaneous tunnel around the back, neck and upper jaw until it was situated just lateral to the orbit. The cat was then placed in a stereotactic head frame and whilst held in the frame manoeuvred so that the ventral part of the animal was uppermost. The orbit of the cat lacks a bony floor (Prince *et al.*, 1960) and the midorbital part of the optic nerve was approached through a simple muscle-splitting incision in the roof of the mouth behind the last molar tooth (*see* Henkind *et al.*,

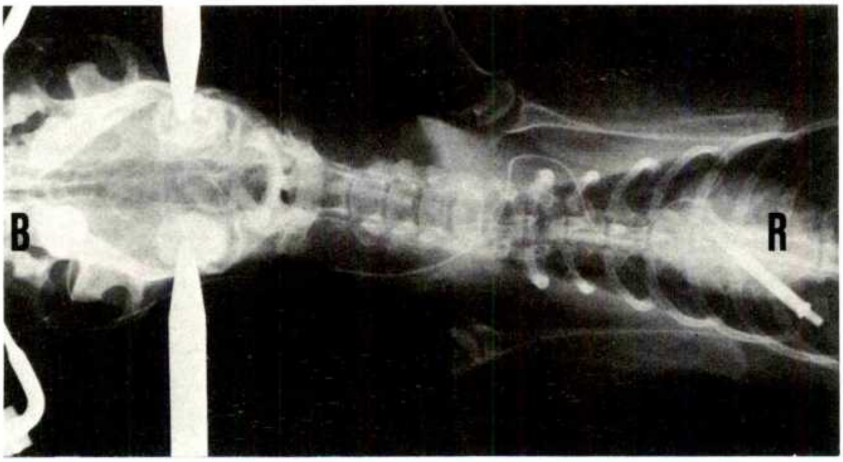

FIG. 1. Radiograph of partially inflated implant positioned in an anaesthetized cat held in a stereotactic frame. The subcutaneous reservoir (R) is connected *via* thin tubing to a silicon rubber balloon (B) which lies close to the optic nerve in the orbit. The implant contains radio-opaque dye.

1975). With the nerve exposed the balloon was pulled through into the orbit from its previously prepared position and placed alongside the posterolateral aspect of the optic nerve where it was held by the muscle cone surrounding the nerve. Care was taken to avoid trauma to the optic nerve and its blood supply during the dissection. The visual evoked potential and electroretinogram from the operated eye were monitored throughout the implantation procedure. The muscle layers of the orbital floor were drawn together and the skin incisions closed.

Method of Compression

The optic nerves in the experimental animals were subjected to the neighbourhood effects of the implants in one of three ways. In 4 animals (B11, B18, B21 and B8) the balloon was left uninflated but adjacent to the nerve. The optic nerves from 9 cats (B12, B10, B6, B5, B20, B4, B14, B7 and B29) were subjected to incremental chronic compression. The balloon was implanted uninflated and then progressively inflated by injections of radio-opaque dye (Hypaque 65%) at intervals during the course of the experiment. In B12, 0.35 and 0.1 ml of Hypaque were injected seven and eleven days respectively after implantation, and in each of the remaining 8 animals in this group four injections of 0.2, 0.1, 0.1 and 0.05 ml were made serially on days 7, 14, 21 and 28 respectively of the experiments. In the third group of animals (B23, B19, B27 and B26), the balloon in each experiment was inflated by a single injection of 0.25, 0.45, 0.3 or 0.25 ml of dye at or soon after implantation and no further injections made. Each injection was made percutaneously into the reservoir during a short anaesthetic. X-rays (fig. 1) taken at regular intervals during the experiments showed that the balloon remained inflated between the injections and between the final injection and the time of perfusion. Any animal in which the balloon leaked at the time of injection or when removed after perfusion was excluded from the study. In addition to the immediate increase in balloon size following each injection, radiography showed a further increase between injections and after the final injection. This additional increase is presumed to have been caused by fluid moving from the orbital tissues into the balloon through its walls under osmotic forces. The implant thus remained inflated and acted as an expanding orbital mass during the course of the experiment.

Controls

Five cats were used as controls to study the effect on the optic nerves of the orbital operation. All animals underwent a procedure identical to that in the experimental group with exposure of the optic nerve in its midorbital course. One cat (C1) was allowed to recover after a sham operation in which a balloon was placed beside the optic nerve and then immediately removed. In the other 4 control cats the balloon was implanted in the orbit but outside the muscle cone and therefore several millimetres from the nerve. The balloon in cat C2 remained uninflated, in C3 and C4 it was inflated by increments and in C5 it underwent a single inflation immediately after implantation. The animals C1, C2, C3, C4 and C5 were examined after 22, 166, 36, 103 and 7 days, respectively.

Histology

The cats were killed under anaesthesia by perfusion with 1 per cent glutaraldehyde and 2 per cent formaldehyde in a phosphate buffer after experiments lasting from 2 to 176 days (*see* Table 1). Perfusion of the head was carried out by flow from the thoracic aorta and the optic nerves removed by ventral dissection of the skull (*see* Eames *et al.*, 1977 for details). Each nerve was cut transversely into 1 mm blocks along its length and placed in 3 per cent buffered glutaraldehyde for 2 h and then for a further 2 h in 2 per cent aqueous osmium tetroxide; 1 μm sections from each plastic embedded block were stained with toluidine blue for light microscopy. Blocks were remounted to permit longitudinal sections to be cut. For electron microscopy thin sections from selected areas were stained with uranyl acetate and lead citrate. The length of the lesion in each compressed nerve was measured by following the histological changes through the series of transverse blocks and the cross-sectional area of nerve involved was estimated from tracings of photomicrographs of transverse sections.

An index of the degree of compression of the nerve by the balloon was made by calculating the ratio of the cross-sectional area of the whole nerve at the site of the lesion to the mean of the areas of the nerve immediately distal and proximal to the lesion. Along corresponding lengths of noncompressed nerve the area varied by less than 12 per cent. A ratio of 0 88 or less therefore implied compression of the nerve.

Nodal Frequency Analysis

Electron micrographs of longitudinal sections through selected lesions were arranged into montages and submitted to quantitative analysis in order to compare the frequency of nodes along fibres of different myelin sheath thickness. Four observations were made on each length of fibre within the montage: (1) the length of fibre; (2) the presence or absence of a node of Ranvier; (3) the type of myelin sheath—this was judged to be normal or inappropriately thin depending on whether the ratio, g, of axon diameter to external fibre diameter was below or above 0.85 (*see* Waxman, 1978); and (4) the external fibre diameter. The axon and external fibre diameters of a fibre were taken as the mean of several equally spaced measurements along the length of fibres whose axes approximated to the plane of section or the largest diameters of fibres cut obliquely. The data were analysed on the University of London CDC 6600 computer. The number of nodes on the two types of fibre were counted and allocated to three external fibre diameter groups (0–2 μm, 2.1–3.0 μm and > 3.0 μm). The total length of fibre observed in each of the three diameter groups was computed and the number of nodes per unit length calculated. Two way analyses of variance were carried out for each cat using the SPSS version 7 program with external fibre diameter and fibre type being the two variables. The data for all animals were also combined in a three way analysis of variance with the individual cats being the third variable.

Clinical Observations

These were made before and after the implantation procedure, at each change in balloon size and immediately prior to perfusion. The degree of proptosis or ptosis, pupil size, pupillary light responses, presence or absence of a relative afferent pupillary defect (RAPD) (Thompson, 1966) and the fundal appearance were noted. The last two observations were made in anaesthetized animals. Pupillary deficits were classed as moderate if there was a clear RAPD but no defect of the direct light response or severe if there was a marked RAPD and a defect of the direct light response.

RESULTS

Morphological Observations

Control nerves. The operated nerves of the 5 control cats showed no histological differences from the normal nerves. It was thus concluded that the orbital dissection including the placement of the balloon had not damaged the nerves. In addition the optic nerves contralateral to the side of operation in both control and experimental animals were normal.

Experimental nerves (Table 1). When the optic nerve was exposed after perfusion it was displaced from its normal course by the balloon and in 13 out of 17 cats the nerve was narrowed at the site of contact with the balloon. In 11 out of 13 animals with an inflated implant measurement of the compression index (*see* Methods) confirmed that the nerve had been compressed. Histological abnormalities were found in all nerves when the balloon, either inflated or uninflated, remained implanted immediately alongside the nerve. The characteristic lesion in nerves compressed for less than six weeks was a focal area of damage localized to the border of the nerve adjacent to the balloon. Histological abnormalities extended for only 1 to 2 mm along the nerve and occupied less than 10 per cent of its cross-sectional area. The only exception was a large lesion in cat B19, in which the balloon had been fully inflated by a single injection at the time of implantation. In the longer term experiments the lesions remained small if the balloon was uninflated but tended to be larger if the balloon was inflated, extending up to 9 mm along the nerve and occupying over 50 per cent of its cross-sectional area. The number of injections used to inflate the balloon had no consistent effect on the size of the lesion.

TABLE 1. CHARACTERISTICS OF LESIONS AND ASSOCIATED DEFICITS IN PUPILLARY LIGHT RESPONSES IN 17 IMPLANTS

		*Lesion characteristics**				*Pupil deficit*	
Cat. No.	*Implant duration (days)*	*Length affected (mm)*	*Area*	*Histological type*	*Compression index*	*Degree*	*Onset (days)***
B11	2	2	+	D	0.98	None	—
B18	7	1	+	D	0.92	None	—
B23	7	2	+	D	0.77	None	—
B19	11	5	+ + +	W	0.59	Severe	After 4
B12	21	1	+	P	0.79	None	—
B21	33	2	+	R	0.98	None	—
B10	36	2	+	R	0.81	None	—
B6	47	5	+ + +	P	0.80	Severe	14–21
B27	52	2	+	R	1.0	None	—
B5	72	2	+	R	0.9	None	—
B20	86	6	+ + +	R	0.79	Severe	14–21
B4	87	9	+ +	R	0.82	Moderate	21–28
B14	98	2	+ + +	P	0.80	Severe	After 28
B8	108	2	+	P	0.88	None	—
B7	133	3	+ +	R	0.83	None	—
B29	140	2	+ + +	R	0.67	Moderate	21–28
B26	176	4	+ +	R	0.77	Moderate	After 28

*Maximum cross-sectional area of nerve involved: + = < 10 per cent; + + = 11–50 per cent; + + + = > 50 per cent. D = demyelination; W = degeneration; P = partial demyelination; R = remyelination and partial demyelination. Compression index = ratio of cross-sectional nerve area at site of lesion to mean of areas proximal and distal to lesion (*see* histology methods). ** Time interval between which onset of deficit in pupillary light response occurred.

Histological changes (*first eleven days*). Four animals were examined within this period. In cats B11 and B18 the implant was left uninflated whereas in B23 and B19 the balloon was inflated at the time of the initial operation. The predominant pathological process in the three focal lesions (cats B11, B18 and B23) was one of demyelination with either complete or partial loss of the myelin sheath of the fibres from around intact axons (fig. 2). Fibres of all diameters were affected. At two days the demyelination process involved isolated fibres separated by normal surviving fibres. Some fibres showed only disorganization of their inner cytoplasmic tongues

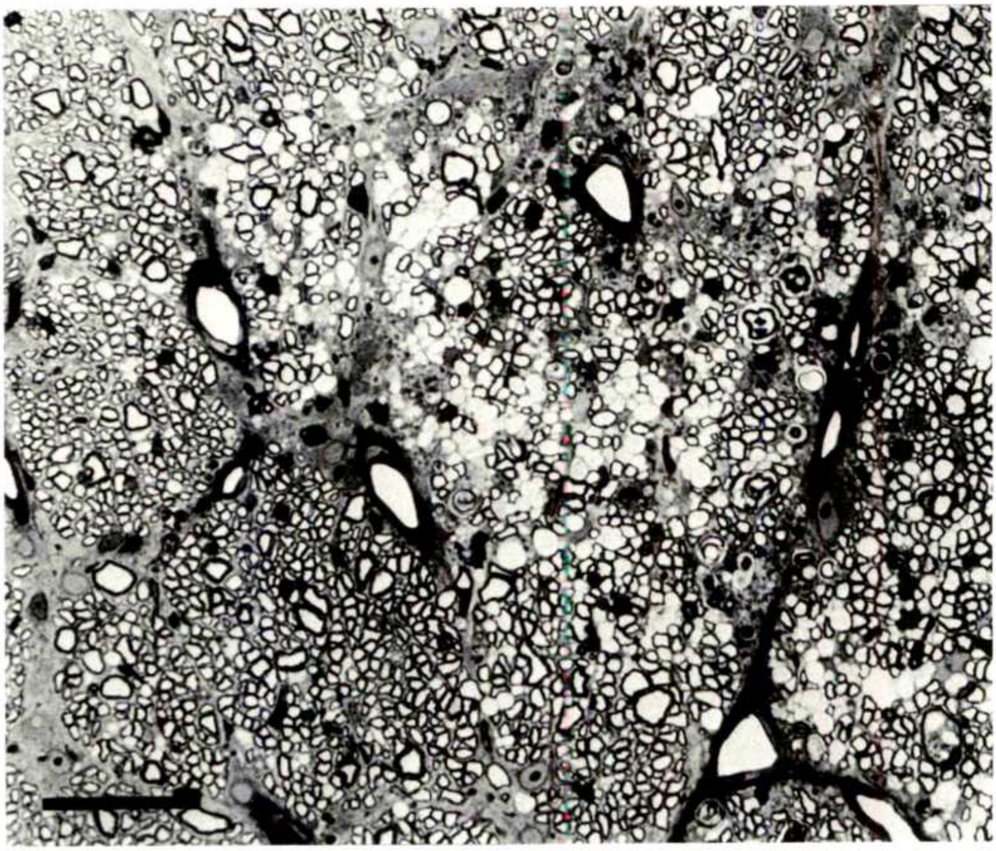

FIG. 2. Transverse section of part of optic nerve adjacent to balloon in 7-day animal (B18). Groups of completely demyelinated axons are seen. Light micrograph. Bar = 50 μm.

and a few adjacent lamellae, while other fibres had little or no remaining myelin and their axons were either bare or in contact with a vesicular network of disrupted lamellae (fig. 3). Many phagocytic cells were observed in close relationship to the demyelinated fibres, sometimes with their nuclei within the separated myelin sheath (fig. 4). The ultrastructure of the phagocytes resembled that of microglial cells (Blakemore, 1975), but we did not attempt further identification of their origin.

By seven days, although a few fibres with only partial thickness loss of myelin were seen, the lesion was generally more advanced with completely demyelinated axons occurring in groups (fig. 2). The plasma membranes were often closely applied but no specialized contact areas were found and in places the axons were separated by astrocytic or phagocytic processes. There was marked proliferation of astrocytic processes whereas oligodendrocytes appeared depleted in numbers. In longitudinal

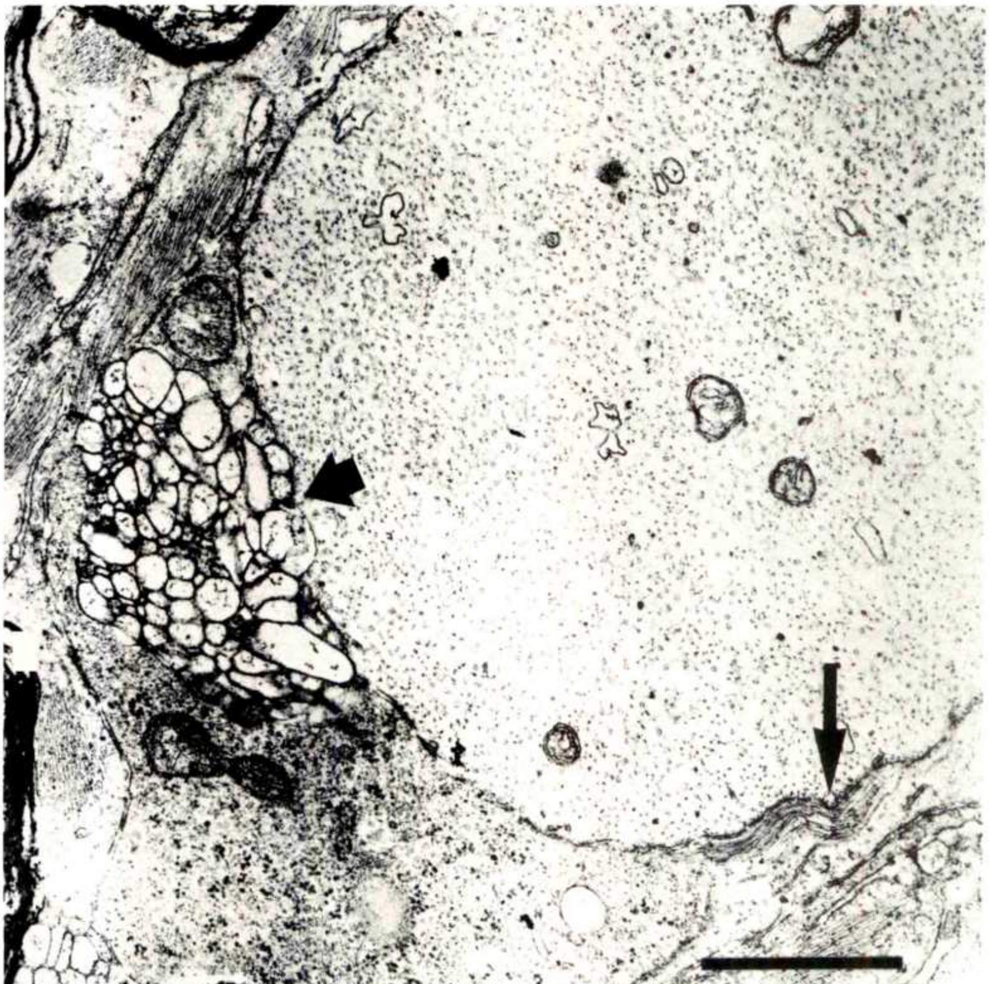

FIG. 3. Electron micrograph of transverse section of fibre in 2-day cat (B11). The fibre is almost completely demyelinated; fragments of some lamellae remain (long arrow), others form a vesicular network in contact with the axon (short arrow-head). Bar = 1 μm.

sections it could be seen that the myelin loss was related to the nodes of Ranvier with widened nodal gaps common and intact paranodes abutting long lengths of completely demyelinated axons (fig. 5). Because of their small diameter it has not proved possible to tease cat optic nerve fibres and we were therefore unable to establish whether the demyelination was confined to the paranodal region or could involve a whole internode.

Only a few fibres in these three focal lesions degenerated completely but in the extensive lesion produced in cat B19 by a one-stage inflation of the balloon, most

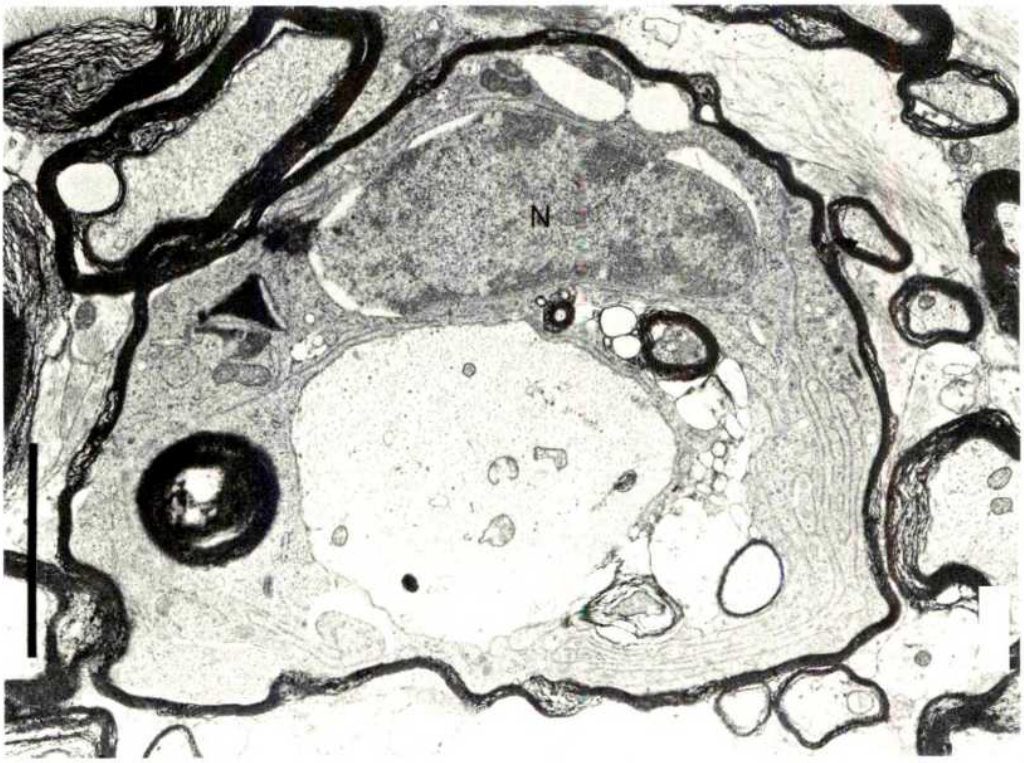

FIG. 4. Electron micrograph of transverse section of another fibre in 2-day cat. A phagocyte nucleus (N) is seen within the myelin sheath which is separated from the axon by cytoplasm containing debris. Bar = 1 μm.

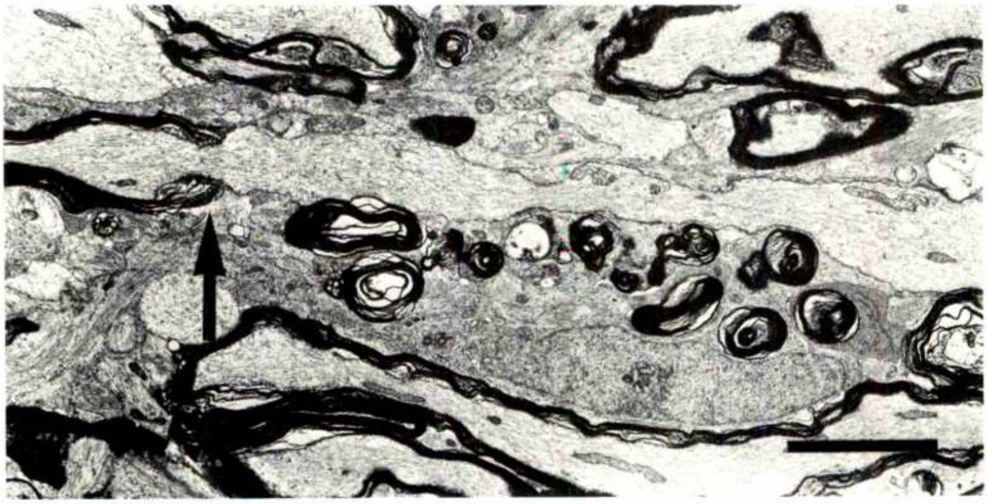

FIG. 5. Longitudinal section of optic nerve at seven days (B18). An intact paranode (arrow) abuts a length of completely demyelinated axon. Myelin debris is present below the axon. Electron micrograph. Bar = 5 μm.

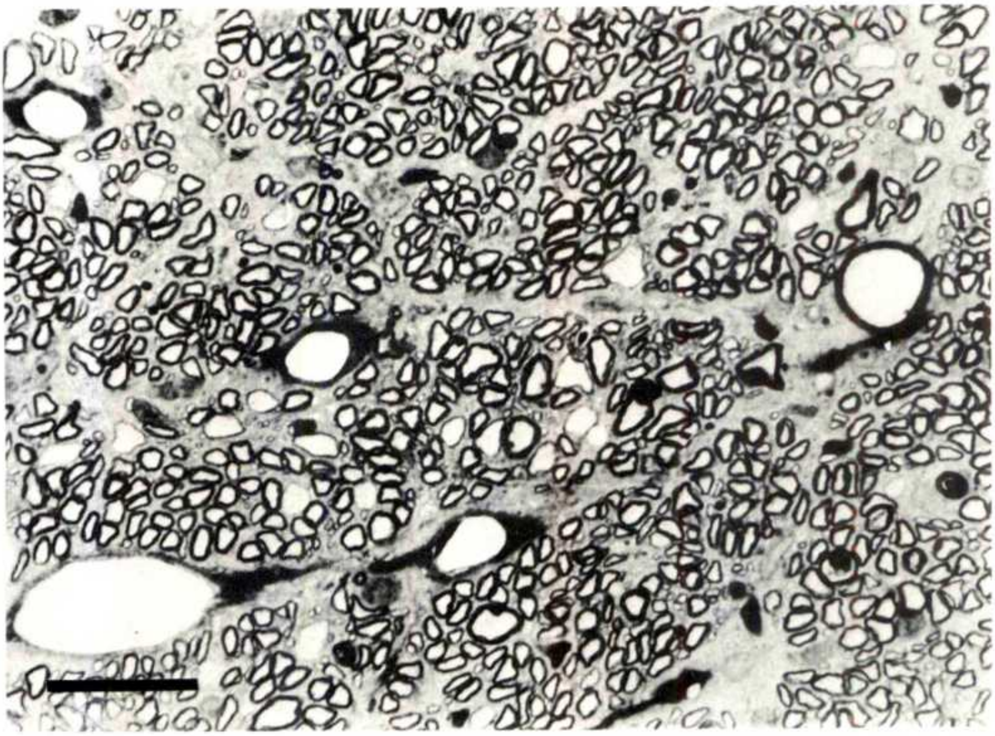

FIG. 6. Light micrograph of transverse section of compressed optic nerve of cat at 86 days (B20). There are large angular thinly myelinated fibres scattered singly or in small groups among the normal fibres. The thinly myelinated fibres distributed in this pattern represent partially demyelinated fibres (*see text*). Bar = 25 μm.

affected fibres were undergoing degeneration and demyelination was confined to a few fibres at the edge of the lesion.

Histological changes (*21 to 176 days*). The 13 optic nerves examined after compression for 21 to 176 days all showed myelinated fibres with myelin sheaths which were inappropriately thin for the diameters of the axons they contained. In transverse sections the thinly myelinated fibres had two distinct patterns of light microscope appearances. One pattern (fig. 6) consisted of single large (> 3 μm) angular thinly myelinated fibres (P fibres) scattered among normal surviving fibres; the other (fig. 7) was of rounded thinly myelinated fibres (R fibres) occurring together in groups of similar fibre diameter. The axon diameters of the R fibres tended to be smaller than those of the surrounding normal fibres. The ultrastructure of the R and P fibres and the different organization of their thin myelin into internodes (details *below*) showed that they represented remyelinated and partially demyelinated fibres, respectively.

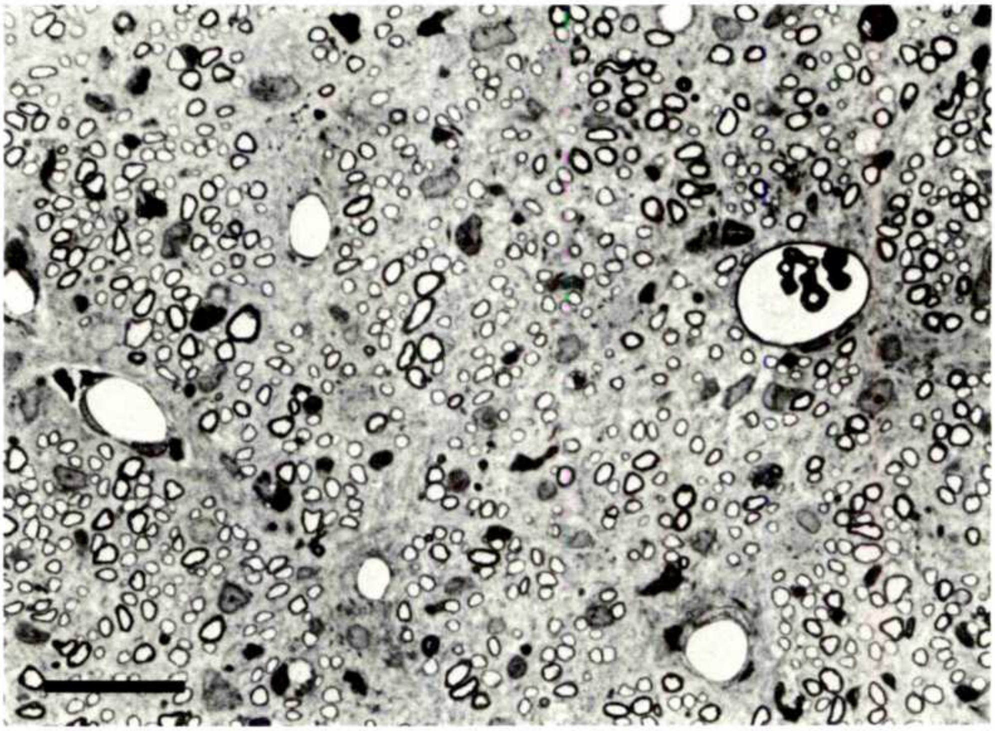

FIG. 7. Light micrograph of transverse section of lesion in 87-day animal (B4). Thinly myelinated fibres are seen together in groups. Profiles of the fibres are rounded and their axon diameters are smaller than those of the surrounding normal fibres. This pattern of fibres is characteristic of remyelinated fibres (*see text*). The figure also shows considerable gliosis. Bar = 25 μm.

Partially demyelinated fibres were seen in all animals and, in addition, remyelinated fibres were observed in 9 out of 13 cats. The two sorts of fibres in these 9 animals usually occurred at different but adjacent regions along each nerve, but in four the areas where the two fibres were observed overlapped. The presence of remyelination was not clearly related either to the duration or method of optic nerve compression or to the size of the resulting lesion (Table 1). A variable but usually small number of fibres within each lesion degenerated. Degenerative changes were most marked in 4 long-term animals (B20, B14, B4 and B26) with extensive lesions, and in cat B4 there was quite marked gliosis (fig. 7). Although gliosis was only mild in the lesion illustrated in fig. 6, P fibres could not usually be distinguished from R fibres by the extent of the associated gliosis.

Remyelinated fibres. The earliest R fibres were seen in the 2 5-week animals. In the 10 to 13-week cats the myelin sheaths were thicker than at 5 weeks but were still inappropriately thin, and there was no further increase in myelin thickness in the longer term lesions. The electron microscopic appearances of the R fibres were characteristic of remyelinated fibres (Harrison *et al.*, 1972*a*) with small numbers of myelin lamellae in regularly arranged complete spirals around the axons in transverse sections (fig. 8) and with uniformly thin internodal myelin in longitudinal sections. Uncompacted myelin lamellae were seen around some fibres.

Confirmation that the R fibres represented evidence of remyelination depended on showing that the thin myelin was organized into the short internodes characteristic of remyelinated fibres (Gledhill *et al.*, 1973; Blakemore and Murray, 1981). Because of the technical problems of cutting adequate lengths of fibres in accurate longitudinal section, micrographs of complete internodes were not seen either in control optic nerves or in fibres of normal myelin thickness in the compressed optic nerves. However, complete internodes were identified on the thinly

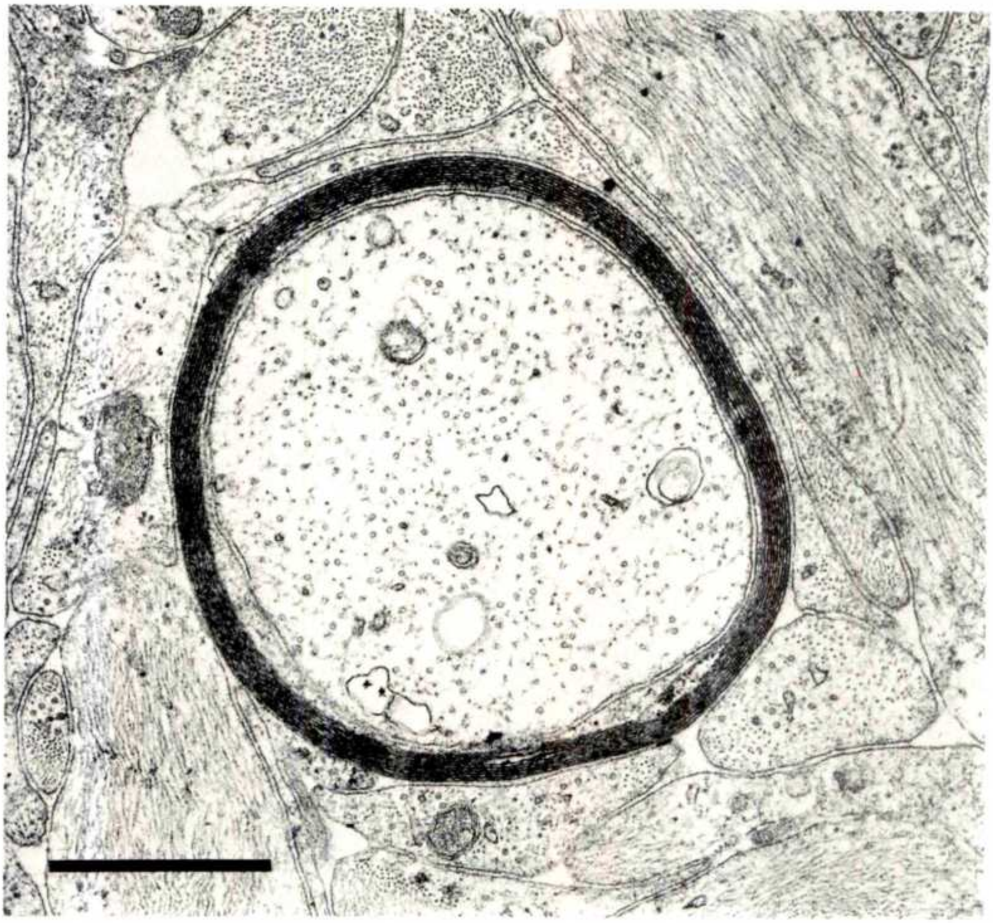

FIG. 8. Electron micrograph of transverse section of remyelinated fibre in 87-day cat. The myelin sheath is inappropriately thin for the diameter of the axon. The fibre is surrounded by astrocytic processes containing filaments. Bar = 1 μm.

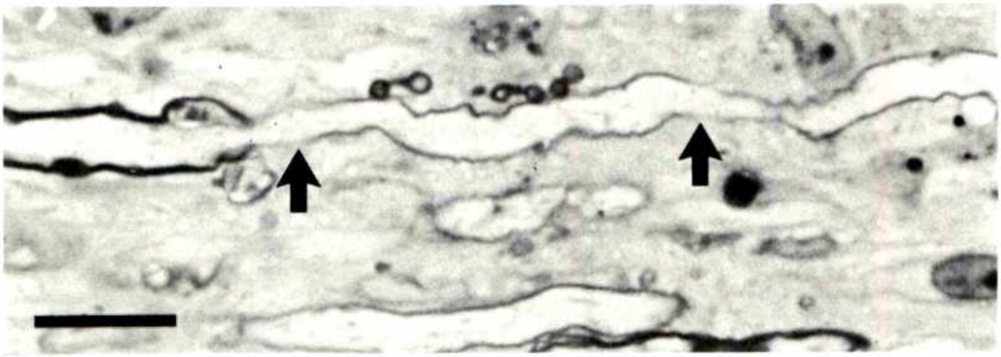

FIG. 9. Longitudinal section through an optic nerve of cat compressed for 36 days (B10). A thinly remyelinated internode is shown, measuring 30 μm between the two nodes (arrows). Light micrograph. Bar = 10 μm.

myelinated R fibres in 7 out of the 9 lesions containing these fibres (fig. 9). Forty-seven whole internodes were seen and these ranged in length from 4 to 96 μm (mean 30.4 μm, SD ± 22.4 μm); lesions of all durations contained a wide range of internodal lengths and very short internodes (< 25 μm) were still observed in the optic nerve compressed for twenty-five weeks. Because teased fibre preparations could not be obtained additional evidence for the presence of short remyelinated internodes was sought from the results of nodal frequency analyses carried out on 3 cats, B10, B4 and B26. (*see* Methods). The data from the 3 animals are shown in Table 2. In cats B10 and B26, nodes were significantly more frequent on the thinly myelinated, R fibres, than on the normally myelinated fibres ($F = 45$, $P = 0.02$ and $F = 42$, $P = 0.02$, respectively). In the third animal (B4) the difference just failed to reach significance ($F = 14$, $P = 0.06$). However, when the data from all 3 animals were analysed together, the difference in nodal frequencies became highly significant ($F = 90$, $P = 0.00001$). We conclude that the R type thinly myelinated fibres have remyelinated. The combined analysis also showed significant differences in nodal frequencies on fibres of different diameters ($F = 15$, $P = 0.0005$).

TABLE 2. COMPARISON OF NODAL FREQUENCY ON NORMALLY AND THINLY MYELINATED FIBRE

	External fibre diameter								
	0-2 μm			*2.1-3.0 μm*			*> 3 μm*		
	B10	*B4*	*B26*	*B10*	*B4*	*B26*	*B10*	*B4*	*B26*
Normally myelinated fibres ($g \leq 0.85$)									
No. of nodes observed	3	2	3	4	3	2	3	4	3
Total length of fibres observed (μm)	881	322	361	4126	1653	697	3845	4845	1718
No. of nodes per 10000 μm	34	62.1	83.1	9.7	18.1	28.7	7.8	8.3	17.5
Thinly myelinated fibres ($g > 0.85$)									
No. of nodes observed	16	17	54	26	43	44	13	11	12
Total length of fibres observed (μm)	800	791	3133	2107	3544	4520	1156	1713	890
No. of nodes per 10000 μm	200	214.9	172.3	123.4	121.0	97.3	112.4	64.2	134.8

The ultrastructure of the nodal regions of the remyelinated fibres were similar in the 9 cats, and usually resembled that of nodes of Ranvier in the developing CNS of normal animals (Peters, 1966; Hildebrand, 1971). The myelin lamellae ended in the decremental zone of the paranode in a regular arrangement of large tubule-rich cytoplasmic pockets, most of which were in contact with the axolemma often with associated transverse banding of the outer leaflet of the axon membrane. However, modifications of this pattern occurred in up to one-quarter of the remyelinated nodes in each lesion. In some nodes the width of the nodal gap was increased up to 13 μm (fig. 10A) and in others reduced so that no nodal membrane was exposed and adjacent paranodes abutted, forming a 'pseudonode'. Variations also occurred in the paranodal regions themselves. In some fibres the outer myelin lamellae formed terminal loops on the external surface of the tapering myelin sheath and overlay the region where the inner lamellae ended in normal internal loops (fig. 10B). In other fibres the paranode had an interrupted arrangement of cytoplasmic pockets with premature termination of external or internal, or of both groups of myelin lamellae (fig. 11A, B). The total length of such a paranode never exceeded 10 μm and premature termination of lamellae was not observed on internodal parts of the remyelinated fibres. These modifications of the terminal loops were either confined to, or were much more extensive in, one of the two paranodes forming the node. The asymmetry of the node was not, however, related to the orientation of the fibre along the compressed nerve and nodal invagination of the type described in acutely compressed peripheral nerves (Ochoa *et al.*, 1972) was not seen. Other atypical paranodal appearances suggested breakdown of the remyelinated sheaths. This process mainly but not exclusively involved the very short (< 25 μm) internodes. Some myelin lamellae were disrupted and formed myelin figures near the short internodes. Other lamellae with their terminal pockets were detached from the axon in association with astrocytic processes. In fig. 12 the process involved was derived from the astrocyte which formed the perinodal foot processes of the adjacent node. Astrocytic processes were also seen interposed between the axons and terminal myelin pockets of normally myelinated fibres.

Partially demyelinated fibres. P type thinly myelinated fibres were observed in all animals. The range of morphological change was similar in both the long- and short-term experiments. In transverse sections of the P fibres there was considerable variation in the extent of thinning of the myelin sheath and adjacent bare axons were numerous. Electron microscopy showed many irregularities in the myelin sheaths with loss of lamellar compaction. In longitudinal sections the myelin sheath thinning occurred abruptly along an internode with some inner or, less frequently, outer lamellae ending in small loops (fig. 13). Such internodal transition zones differed from nodes of Ranvier in that they lacked astrocytic foot processes and the axolemma had no dense undercoating or transverse bands. In some instances the thin myelin was intercalated into a normally myelinated fibre, but the thinned sheath more often continued up to a node of Ranvier which, apart from the small number of myelin lamellae involved, resembled a mature CNS node and thus differed from

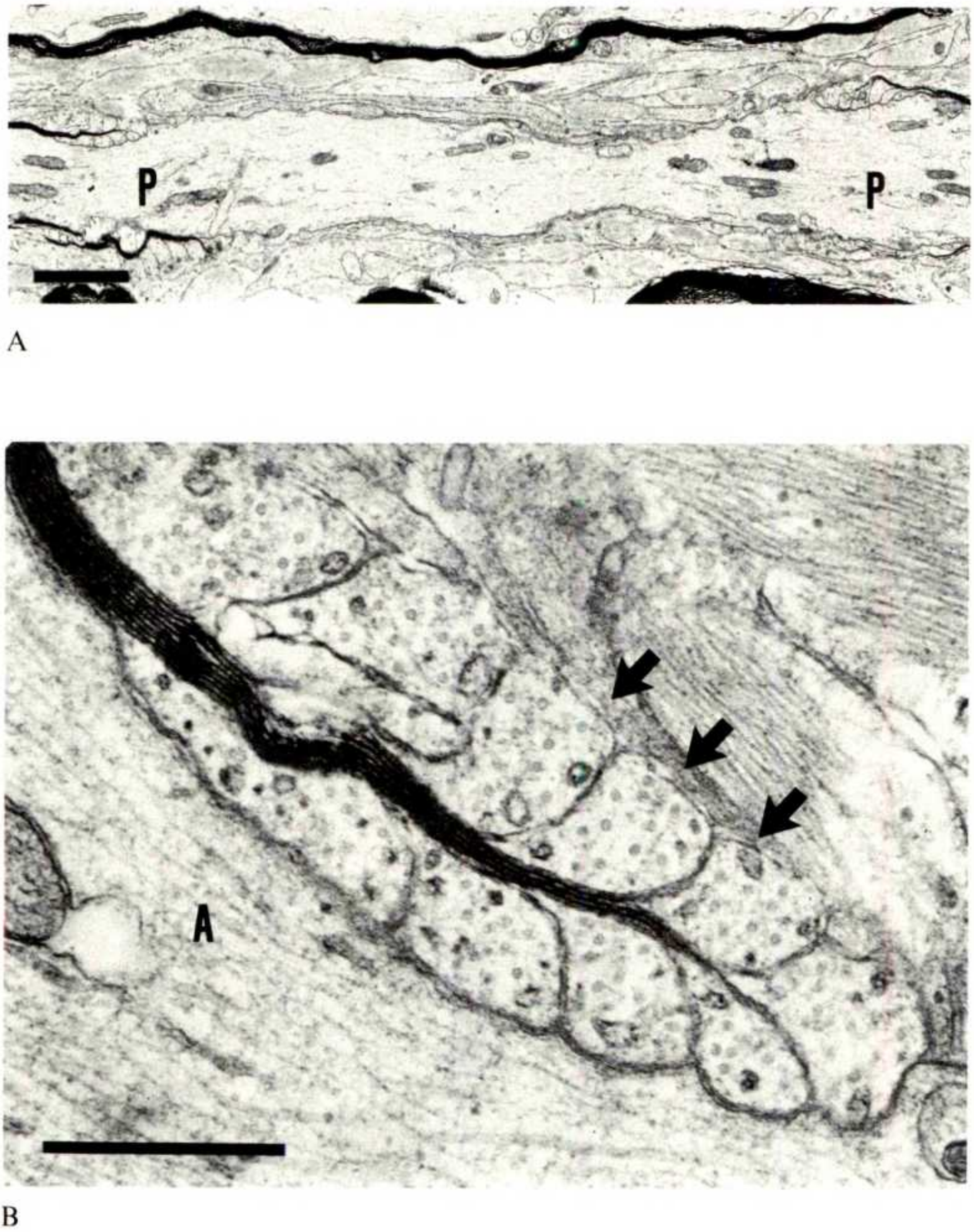

FIG. 10. A, electron micrograph from optic nerve after 86 days. A node of Ranvier is seen in longitudinal section. The nodal gap between the two paranodes (P) is widened to 13 μm. Bar = 2 μm. B, detail of the paranodal loops at the left of the node. Some of the cytoplasmic pockets (arrows) are formed on the external surface of the terminating myelin sheath and do not contact the axon (A). Bar = 0.5 μm.

those on the remyelinated fibres. Some of the thin myelin sheaths were separated from the axons by processes of astrocytes or phagocytes. Short internodes were not observed on any P fibre and a nodal frequency analysis performed on the lesion in cat B14, in which P fibres were the only type of thinly myelinated fibres present, showed no significant difference between these and normal fibres. These structural features are characteristic of partial demyelination (Harrison *et al.*, 1972*b*; Blakemore, 1978) and it was therefore concluded that the P fibres represented partially demyelinated fibres.

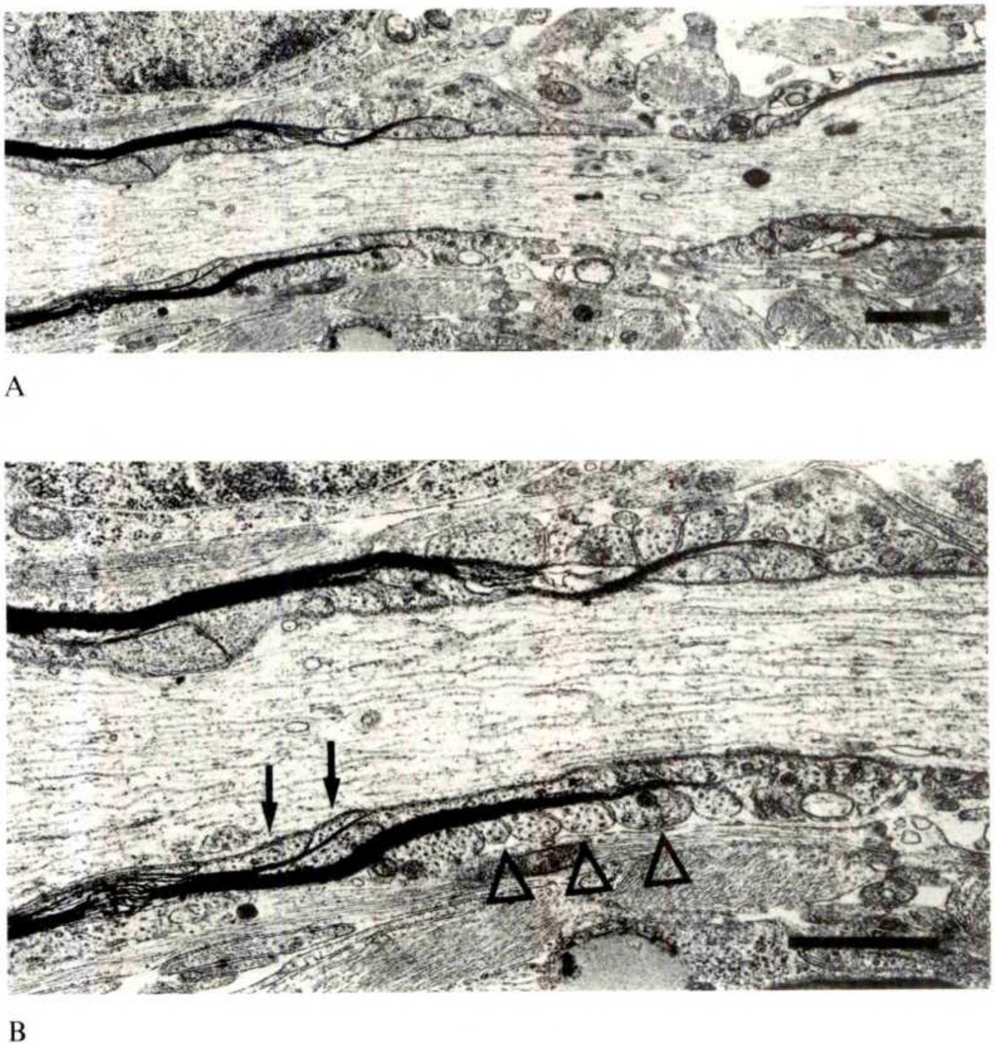

FIG. 11. A, longitudinal section of remyelinated node of Ranvier in 87-day cat (B4). Electron micrograph. Bar = 1 μm. B, detail of paranode at left of node. Some of the myelin lamellae end in premature internal loops (small filled arrows); other lamellae form external loops (open arrow-heads). Bar = 1 μm.

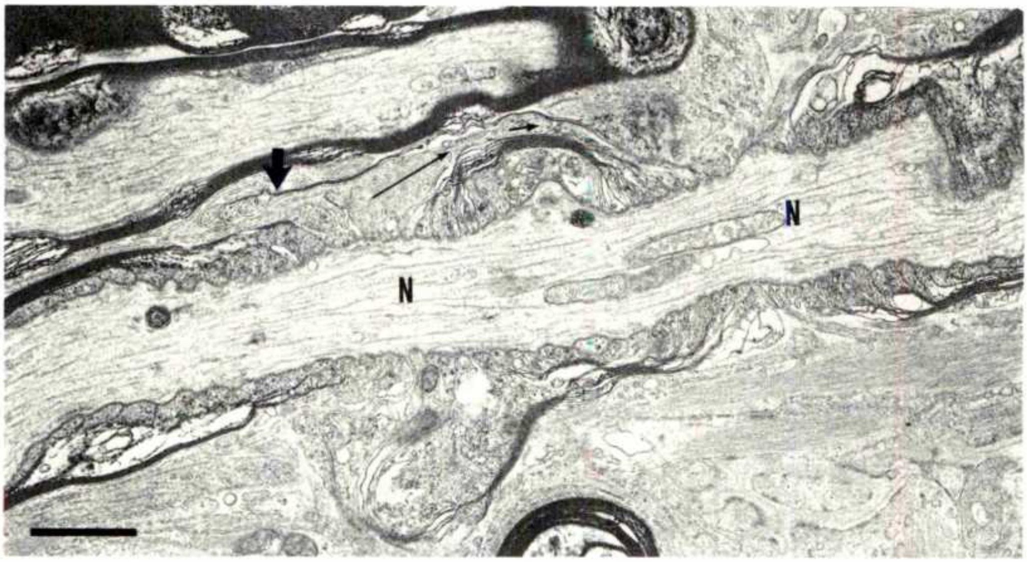

FIG. 12. Electron micrograph of short remyelinated internode in 176-day cat (B26). The myelin sheath between the two nodes (N) is disrupted. A few lamellae (large arrowhead) with their terminal pockets are separated from the axon by an astrocytic process (small arrows) derived from the cell which forms the perinodal foot processes of the adjacent node. Bar = 1 μm.

Cellular appearances (21 to 176 days). As in the earlier lesions proliferation of astrocytic processes occurred in all the compressed nerves and was particularly prominent in areas of fibre loss. Some of the processes were intimately related to partially demyelinated, remyelinated or normal fibres but the majority filled the interstitial regions between the fibres (fig. 8).

Phagocytic cells containing myelin debris and lipid droplets were observed in all lesions. The appearance of oligodendrocytes differed between various parts of the lesions. In areas where partially demyelinated fibres predominated, the oligodendrocytes were not prominent and their cytoplasm contained few mitochondria and only short segments of endoplasmic reticulum, but near the remyelinated fibres the oligodendrocytes were common with each cell extending several narrow processes towards the remyelinated fibres. The latter cells contained cytoplasm with many mitochondria, stacks of rough endoplasmic reticulum and free ribosomes. No lesion contained Schwann cells and none of the remyelinated fibres had any features suggestive of remyelination by such cells (Harrison *et al.*, 1972*a*).

Clinical Observations

Cat B19 developed transient proptosis for 24 h after its balloon was fully inflated but no animal showed any abnormality of the optic fundi, eye movements, lids or pupil sizes. Seven of the 17 animals with compressed nerves developed abnormal

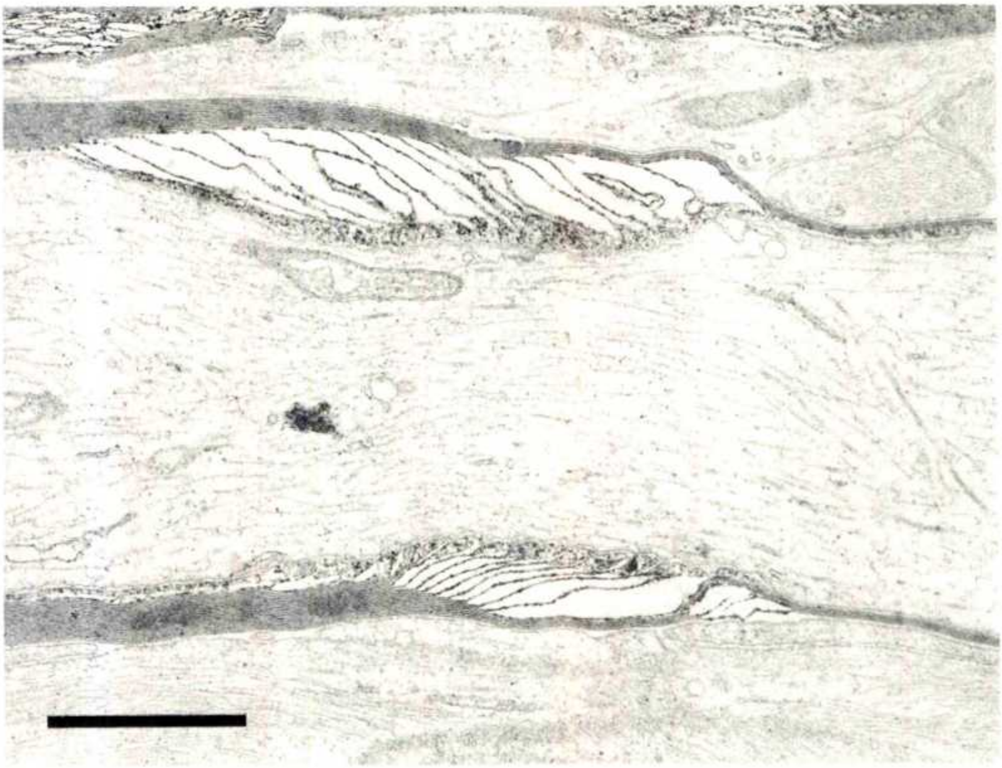

FIG. 13. Longitudinal section of partially demyelinated nerve fibre in 98-day cat (B14) showing an internodal transition zone between thick and thin parts of the myelin sheath. The inner myelin lamellae end in small loops indenting the axolemma whereas a few outer lamellae continue into a sheath of reduced thickness. Electron micrograph. Bar = 1 μm.

pupillary light responses the severity and the date of onset of which is shown in Table 1. No pupil deficit changed in severity over the subsequent course of the compression. The presence of a deficit was related to the size of the lesion. Severe deficits tended to occur in those lesions which occupied at least 50 per cent of the cross-sectional area of the nerve and short (1–2 mm) small ($< 10\%$ in area) lesions spared the pupil.

DISCUSSION

The main features of the present experiments are the predominance of demyelination in the early stages of the development of an orbital mass and the appearance of remyelination despite the continued presence of the mass. The mass was formed by a balloon, initially uninflated and which subsequently increased in size not only immediately after each injection but also, as the radiological observations showed, in the intervals between injections and between the last injection and the perfusion.

The implant thus acted as an expanding mass throughout the course of the experiment. The absence of histological abnormalities in the operated control nerves shows that significant damage was not inflicted during the initial operation. The continued presence of a balloon adjacent to the nerve was necessary to produce a lesion. While recurrent acute damage could have resulted from each injection the lack of histological differences between similar duration lesions produced by single or multiple inflations suggests that chronic effects on the nerve were more important. The range of pathological changes observed with implants of the same type probably resulted from differences in the initial position of the balloon relative to the nerve and the manner in which this relationship changed as the balloon expanded within the orbit. While this variability has some disadvantage in terms of analysis of the mechanisms involved, it has the advantage of simulating the behaviour of orbital tumours in man which may undergo rapid changes in size (Henderson, 1973).

In the peripheral nervous system compression has both direct mechanical (Ochoa *et al.*, 1972; Ochoa and Marotte, 1973) and ischaemic (Gilliatt, 1981) effects on nerve fibres. It seems likely that both mechanisms operated in the present model, but we did not attempt to determine the relative contribution of each to the production of the different types of pathological change. The mechanical effects were probably in part at least due to direct pressure since the cross-sectional area of most of the nerves was reduced at the site of impingement of the mass. Stretching of the nerve may also have contributed. Demyelination is one of the consequences of acute stretch of peripheral nerve (Denny-Brown and Doherty, 1945).

The demyelination in the early lesions resembled that seen in acute cord trauma such as that caused by CSF barbotage (Bunge *et al.*, 1960), screw compression (Gledhill *et al.*, 1973) and dropped weights (Griffiths and McCulloch, 1983). The vesicular pattern of demyelination suggested that the myelin loss did not result exclusively from oligodendrocyte damage but also involved a direct effect on the myelin sheath (Kirk, 1979). Lesions after twenty-one days still contained some completely demyelinated axons, although many fibres had undergone partial demyelination or remyelination. It seems likely that the demyelinated axons in these later lesions represented both persistence of demyelination from the initial phase of compression (*cf.* Harrison and McDonald, 1977) and the breakdown of newly formed sheaths, since stripping and disruption of paranodal lamellae were seen on remyelinated fibres.

Partially demyelinated fibres were prominent in all the later lesions and in 4 cats were the only type of thinly myelinated fibres seen. Persistent partial demyelination occurs after both toxic and compressive lesions of the spinal cord, whether the insult is monophasic (Harrison *et al.*, 1972*b*; Harrison and McDonald, 1977) or persistent as in the experiments of Fish and Blakemore (1983) in which partial demyelination without remyelination was seen in the kitten spinal cord the growth of which was restricted by ligature.

Remyelinated fibres were identified in 9 of 13 nerves compressed for longer than three weeks and were separated either along the length of the nerve or within its cross-section from partially demyelinated fibres. Remyelination of central nerve fibres has been observed after acute cord lesions in adult animals (Bunge *et al.*, 1961; Harrison and McDonald, 1977; Griffiths and McCulloch, 1983), but its occurrence during chronic compression is a new finding in the CNS, although it has been reported on peripheral nerve fibres (Aguayo *et al.*, 1971; Ochoa and Marotte, 1973). The atypical arrangements of the paranodal myelin lamellar loops observed on some of the remyelinated fibres resembled those described by Fraher (1978) during the early stages of myelinogenesis in the CNS. It seems likely that the continued presence of the orbital mass would have encouraged the persistence of such paranodes by restricting the normal maturation in shape of the ensheathing oligodendrocyte process. Similar paranodal appearances have been described in the CNS in congenital dysmyelination (Griffiths *et al.*, 1981) and in remyelination after acute cord trauma (Griffiths and McCulloch, 1983). Complete short remyelinated internodes similar in length to those described in remyelination after acute (Blakemore *et al.*, 1977; Harrison and McDonald, 1977) and chronic (Prineas and Connell, 1979) central demyelinating lesions were seen in plastic sections. The nodal frequency analysis provided evidence that such internodes were common but the method cannot give precise information about the range of lengths of the remyelinated segments. The experiments of Smith *et al.* (1981) have established that secure conduction can be restored through a central lesion in which there is wide variation in remyelinated internodal length. This suggests that the fibres in the present experiments would have been capable of conduction had they been decompressed.

Seven of the animals had pupillary signs of optic nerve dysfunction. Several factors probably contributed to this functional loss. First, there would be pressure block in morphologically normal as well as abnormal fibres, including the remyelinated fibres. Secondly, conduction would be blocked by demyelination (McDonald and Sears, 1970). It is clear from computer simulation of conduction in the peripheral nervous system (Koles and Rasminsky, 1972) that partial demyelination would also interfere with conduction but it is impossible to predict whether the extent of myelin thinning seen in our experiments would block conduction; it seems probable, however, that the partially demyelinated fibres would be more susceptible to the effects of pressure. Finally, wallerian degeneration, although limited in most animals, would contribute to the functional loss.

Relationship to Human Disease

It is now appropriate to consider how far the familiar symptomatology of compression of the anterior visual pathways and the pattern of recovery following its relief (Cushing and Walker, 1915; Kayan and Earl, 1975) can be explained by our present understanding of the pathology and disordered physiology of central nerve fibres. Before doing so, two additional points must be considered. First, there is the question of rapidly reversible conduction block, familiar from the study of peripheral nerve where the mechanism is ischaemic (Lewis *et al.*, 1931). A similar phenomenon can be demonstrated experimentally in acutely compressed central nerve fibres (Gledhill, 1974). Reversal of conduction block can also occur within minutes of the relief of chronic compression; Gutin *et al.* (1980) observed prompt return of the flash visual evoked potential following relief of compression by a craniopharyngioma, and we have elsewhere reported a patient with optic nerve compression by a giant aneurysm in whom there were episodes of intermittent spontaneous return of a previously absent pattern evoked potential in the course of a single recording session (Halliday, 1982; McDonald, 1982). Secondly, there is the question of the pathology of chronic compression of central nerve fibres in man. Focal demyelination was demonstrated by Holmes (1906) in chronic spinal cord compression. It is probable that demyelination also occurs in optic nerves compressed by tumours, and the occasional observation of a prolonged delay in the pattern visual evoked potentials recorded in such cases (McDonald, 1982) suggests that the demyelination may be extensive, as in some of the present experiments. We suggest therefore the following mechanisms for visual loss and recovery. Visual impairment may be produced by a combination of loss of nerve fibres by wallerian degeneration, conduction block due to demyelination and 'physiological block' in fibres that would be capable of conduction if they were not compressed. The latter would include histologically normal fibres and remyelinated fibres. The early very rapid phase of recovery can be accounted for by restoration of conduction in such fibres. The slower recovery seen in the ensuing weeks and months is probably mediated by two processes. First would be progressive remyelination and restoration of conduction, as Smith *et al.* (1981) observed in the spinal cord. Secondly, loss of visual function by wallerian degeneration is probably compensated by adaptive mechanisms similar to those operating in the experiments of Jacobson *et al.* (1979), who demonstrated progressive recovery of grating acuity and contrast sensitivity in the months following destruction of up to three-quarters of the fibres in one optic nerve.

ACKNOWLEDGEMENTS

We thank Professor G. Brindley for advice on the design of the implant, Miss E. Paul for statistical advice, Miss J. Igary, Mr K. Singh and Mr H. Long for technical assistance, and Miss Ann Woolley and Miss Jane Cook for secretarial assistance. The work was supported by the Medical Research Council.

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(*Received June 7, 1984. Revised September 6, 1984. Accepted September 11, 1984*)

Brain (1985), **108**, 263-270

NOTICES OF RECENT PUBLICATIONS

Dandy of Johns Hopkins. By William Lloyd Fox, with the sponsorship of the Congress of Neurological Surgeons. 1984. Pp. 291. Baltimore: Williams and Wilkins. Price £19.00.

Although a variety of centres throughout the world considered the development, or in some instances claimed the development, of neurological surgery, such surgery began in the United States of America in the early years of the twentieth century. This little biography documents the part played in that development by a great neurological surgeon in Johns Hopkins Hospital, Walter Edward Dandy. Johns Hopkins, in the early years of the twentieth century, must have been a most stimulating place. Dandy worked initially in the Hunterian laboratory under Harvey Cushing and he continued in Hopkins when Cushing had left for the east coast. The poor relationship between the two men has remained one of the best-known controversies in the development of neurosurgery. Biographers tend, quite naturally, to be sympathetic to their subjects, and we are probably well advised to read Fulton's biography of Cushing together with this biography of Dandy to achieve a balanced view of the contribution of these two outstanding men.

It is not too late, however, to meet surgeons who lived and worked with Dandy, or for that matter with Cushing. From this short biography and the experience of older neurosurgeons amongst us it is quite clear that in Walter Dandy, neurosurgery had a remarkable technical exponent. It is true, however, that like so many great technical neurosurgeons he had a capacity to underscore what suited him and to conceal what did not. It is also equally clear that the foundation of a large school of neurosurgery was never one of his prime concerns and that he was happiest in personal handling of difficult clinical problems.

The biographer outlines the enormous contribution that he made to neurosurgery from his initial researches on the hypophysis and on the development of hydrocephalus to his contributions to the surgery of tic and of Ménière's disease. The story of the development of ventriculography and the controversies into which it led him is well described. His reluctance to accept arteriography, a reluctance almost comparable to Cushing's attitude to ventriculography, reflects the conservatism which is often a hallmark of the true innovator slightly outside his own field.

Nearly half a century later we have gone beyond many of the stresses which were inevitable components of the lives of those who developed our speciality from the beginning. The difficulties under which they laboured, lack of understanding of the cerebral circulation, problematical anaesthesia, and the continual development of knowledge in clinics other than their own must have imposed great strain upon them. They were, in many instances, intolerant and egotistical men.

From this biography emerges a picture of an intense, hard-working, turbulent surgeon, devoted to his patients and to his juniors, critical of his fellows, impatient of those whose standards he considered inferior to his own, a giant in his own time. Many have subsequently learned much from his technique and example.

Neurosurgery is a small speciality even now, and a closely knit fellowship the world over. This is a little book which every young neurosurgeon would do well to read. It is scarcely overpriced at £19. Dr Fox and the Congress of Neurological Surgeons are to be congratulated upon its conception, and the publishers on the excellence of its production.

LINDSAY SYMON

Intracranial Aneurysms, Volumes 1, 2 and 3. By J. L. Fox. Volume 1: pp. 644. Price DM 390.00. Volume 2: pp. 537. Price DM 420.00. Volume 3: pp. 360 Price DM 320.00. Berlin: Springer.

There must be many neurosurgeons who share with this reviewer an increasing dismay as they struggle to keep up with a literature which is expanding at an accelerating rate. This colossal work is a response to the growing problem of the 'information explosion' as it affects one sector of neurosurgery. Professor J. L. Fox, of the University of West Virginia, assisted by seven contributors, has attempted to bring together in a single book all that is currently known about intracranial aneurysms and their treatment.

The result is a work of monumental proportions which contains an extraordinary amount of information about every aspect of intracranial aneurysms and their management. It is arranged in three volumes of decreasing size. The first volume is devoted to epidemiology, aetiology, related conditions, clinical features and secondary complications including vasospasm and the results of diagnostic investigations. The second volume discusses treatment, and the third volume, which may be considered to be somewhat superfluous, is a summary of case records of different categories of aneurysm culled from the literature. The references are arranged on a chapter by chapter basis and accumulate to over 4,000 for the whole book.

Professor Fox is to be congratulated for his superhuman energy and determination which has led him to create a work which will be of value to neurosurgeons throughout the world as a near-exhaustive mine of information and reference. As is only fitting for a work of this scope, this book is beautifully produced and printed and sumptuously illustrated The text is sensibly arranged and, considering the quantity of compressed information it contains, reasonably easy to read, although in some chapters the reader will be slowed down by his efforts to decode a rather complex system of abbreviations and symbols

As a review of the accumulated knowledge on this important subject, this book could hardly be bettered. Its purchase is recommended to every neurosurgical library and to every neurosurgeon who has a serious research interest in this complex subject. Although the growth of knowledge will inevitably lead to parts of its contents being superceded within a relatively short time, it will stand for many years as a comprehensive repository of much secure knowledge that has accumulated up to the present time.

R. S. MAURICE-WILLIAMS

The Eye in General Medicine. Edited by F. Clifford Rose. 1983. Pp. 514. London: Chapman and Hall. Price £29.50.

In a forward to a book entitled *Ophthalmic Manifestations of Systemic Vascular Disease* by D. G. Cogan, Lloyd H. Smith wrote 'There are two organ systems which are readily examined by direct visualization, the skin and the eye. The eye is admirably adapted to direct examination. The structures which admit light to stimulate the retina, an exteriorized portion of the central nervous system, can equally transmit light back to the eye of the observer. In a sense, vision allows visualization. Nowhere else can the structures of an organ be readily examined during life.'

The Eye in General Medicine edited by F. Clifford Rose is a new volume published with the intent of updating readers in the most rapidly growing areas of a multidisciplinary subject. The information presented by both British and American contributors is directly pertinent to the practice of internal medicine, ophthalmology and neurology.

Part One is concerned with general diagnostic aspects of value to the general physician or internist. It covers tests of visual function and the symptoms and signs of ocular hysteria, the merits of computerized tomography and the role of adequate genetic counselling in the prevention of genetically determined ophthalmological disease. This section also contains a chapter on pigmentary retinopathies and one on the virtue of fluorescein angiography. However, given that many potential purchasers of this book may turn to it for practical advice on the causes and management of ocular stroke, and given that much of the material in Part One has already been published elsewhere, I was surprised to find no mention of amaurosis fugax, ischaemic optic neuropathy, retinal emboli or the investigation of central retinal artery occlusion and retinal vascular insufficiency which may occur in patients with extensive extracranial artery disease.

Part Two, the largest single section of the book, deals with neuro-ophthalmology. The contributors of this section have been well chosen. It documents disorders of eye movements as well as cerebral disorders and head trauma. Nystagmus, a major sign in clinical neurology and a difficult topic to discuss, is lucidly and succinctly presented with important emphasis on drug-induced nystagmus, and on ocular bobbing and other distinctive spontaneous eye movement disorders This section also contains a welcome review, well illustrated, on eye movement disorders in basal ganglia disease, diffuse brain diseases presenting as dementia and a chapter on cerebral disorders of visual function. An additional merit of Part Two is the critical discussion of the literature and an updated reference list.

Part Three deals with general aspects of immunology and infections, as well as uveitis with data relevant to sarcoidosis It predates recognition of the ocular complications of the acquired immune deficiency syndrome.

Part Four deals with vascular disorders, especially giant cell arteritis and retinal vasculitis, both idiopathic and associated with systemic disease and hypertension. Part Five relates to endocrine diseases, including diabetes mellitus, thyroid disorders, and inborn errors of metabolism. Part Six reviews skin disorders, common and rare.

Inevitably, in a book containing 24 chapters covering a wide range of topics, they are of mixed quality and interest but overall the editor's aim has been achieved. The book should be available to, and at least selectively read by, all with an interest in the eye as 'the mirror reflecting the body's health'.

SHIRLEY H. WRAY

Metabolische und entzündliche Polyneuropathien. Edited by F Gerstenbrand and B. Mamoli. 1984. Pp. 325. Berlin: Springer. Price DM 148.00.

This book records the proceedings of a conference on metabolic and inflammatory polyneuropathies held at Vienna in Autumn 1983. The principal aim of the meeting was to bring together an international group of research workers with wide interdisciplinary interests in order to exchange views. The 49 papers presented (mostly in German) cover a large number of clinical, electrophysiological, genetic and histopathological studies. Special attention is paid to problems of therapy

The papers are brief but, on the whole, the authors present a comprehensive and critical analysis of their respective fields. The book refers to modern trends in diagnosis and therapy and underlines the important relationship between primarily internal diseases and secondary neurological consequences which require interdisciplinary cooperation.

The wide variety of themes presented, together with the extensive bibliography provided at the end of each paper, make this a valuable reference book, not only for neurologists, neuropathologists and neurosurgeons but also for all those interested in this common group of diseases from the viewpoint of internal medicine or other medical disciplines.

R. WARZOK

Differential Diagnosis in Neuropsychiatry. By Jeremy K. A. Roberts. 1984. Pp. 377. Chichester: John Wiley. Price £17.00.

In recent years new developments in neurology and psychiatry have rekindled the interest in the areas shared by both specialities and, as a consequence, a number of books dealing with specific problems or general approaches to the subject have become available. This book is another addition intended as a clinical guide for those training in these specialities.

The first half of the book is devoted to the evaluation of the history, examination and laboratory investigations. The second contains chapters on specific topics such as personality change, epilepsy, head injury, aggression, delirium, dementia, states of altered consciousness, catatonia and stupor, sleep disorder and disorders of perception. The book ends with a collection of case histories.

In my opinion the best chapters are those dealing with epilepsy and related disorders and computerized tomography, as they are the author's areas of special interest. I also found the case histories useful and this is something other books on the subject rarely offer. An extensive bibliography is another useful point. Other parts of the book are, however, less satisfactory. At times a tendency to overinclusiveness and unclear layout of information could make it difficult for the uninitiated to separate important facts from trivia. There are also some omissions, minor on the whole, such as paying little attention to tests of memory and other specific cognitive abilities.

Although weak in parts, the good points of the book make it possible to recommend it as a useful introduction to the subject.

MARIA A. RON

The Physiological Basis of Memory. Second Edition. Edited by J. Anthony Deutsch. 1983. Pp. 431. New York and London: Academic Press. Price $49.00.

This is completely rewritten from the first edition, published in 1972, although there is some overlap in the topics considered. These range from biophysical studies of long-term cellular changes to neuropsychological interpretations of lesion effects. The format is that of conference proceedings, with 10 chapters by a total of 14 authors. There is no attempted integration of the approaches illustrated.

Two chapters by Schneider and colleagues, Simson and Plough, on spreading depression and on electroconvulsive shock, are short, to the point, comprehensible and convincing. Their conclusions are not simple or dramatic, but could hardly be so since the argument largely consists of a patient refutation of the simple and dramatic claims of predecessors in these fields. A chapter by Hawkins on cellular neurophysiological studies of learning is thorough and comprehensive. His discussion covers experiments and studies both with vertebrates and with invertebrates. It appears that we shall shortly know the cellular mechanisms of simple associative learning in simple animals, but that studies of the electrophysiological correlates of complex learning in complex animals have told us very little. An equally central topic is covered with almost equal scepticism by Chapoutier, who reviews the search for chemically coded memory traces such as 'catabathmophobin', the putative peptide which encodes step-down avoidance learning. Much the most enjoyable chapter is a ramble round the brain by Susan Iversen, taking in the inferotemporal cortex, hippocampus, amygdala and frontal lobe of monkeys, rats and people. Naturally in such a broad view she cannot fully defend all of her conclusions against other possibilities, but every page is thought-provoking. Unfortunately this chapter is marred by misprints and the reader needs to be constantly aware that, for example, 'alteration' and 'alternation' are interchangeable. This is perhaps a chapter more for the research worker than for the undergraduate, therefore. A chapter by Squire and Zola-Morgan attempts to resolve the well-known paradox that medial temporal lobe ablation produces severe amnesia in man but leaves some memory tasks unimpaired in monkeys. Their attempt relies heavily on the occasional findings of impaired visual discrimination learning in monkeys with hippocampal ablations, findings that seem on the contrary most plausibly attributed to involvement of inferotemporal cortex in those ablations in some experiments. Their review also makes confident but controversial assertions about the neuropathology of human amnesia. It should be read with caution by those unfamiliar with the conflicting views and evidence in this difficult field. A chapter by Quartermain establishes that pharmacological manipulation of catecholamines has effects upon a wide variety of learning and performance measures in rats. Gallistel reviews self-stimulation. Deutsch gives a detailed account of his own experiments from the 1960s, drawing inferences about memory consolidation on the basis of some simple assumptions that seem difficult to reconcile with Schneider and Plough's contention that post-training treatments affect both consolidation and retrieval. Martinez, Jensen and McGaugh give a broader coverage of drug effects that facilitate learned performance.

All these contributions are concerned with topics arguably relevant to the physiological basis of learning and memory, but it is difficult to see what area of brain research could not have been eligible for inclusion by that broad criterion of acceptance. As Hawkins notes, all areas of the brain probably play some role in learning and memory. Further progress in this field will therefore proceed together with progress in general physiological psychology, rather than by the use of any special single techniques; the only obvious cohesive factor among the contributions to this volume is that on the whole they are concerned with techniques that seemed more promising, and more specifically relevant to the study of the physical memory trace, in 1972 than they do now.

D. GAFFAN

Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives. Edited by Barry L. Jacobs. 1984. Pp. 248. New York: Raven. Price $61.50.

This well-planned volume contains invited articles dealing with different aspects of the psychopharmacology of hallucinogenic drugs, and it provides an excellent summary of the present state of knowledge regarding their mode of action. The approach is interdisciplinary and the editor has chosen his contributors well since the different articles are finely matched stylistically and yet overlap is minimal. Each chapter is detailed enough for specialists but starts at an introductory level, and all of them should be accessible to readers without expert knowledge of the topic covered. The emphasis is on indolealkylamine compounds, especially LSD and related substances: phencyclidine and its congeners are also included but less comprehensively, as is perhaps appropriate in view of the rather lesser amount of information available.

The book starts with a chapter which covers the historical, botanical and religious background to the present-day interest in hallucinogens. There is also a brief review of the main pharmacological effects in humans. These articles appropriately set the scene for the core section of the book, which consists of six chapters on the behavioural, neurochemical and neurophysiological effects of hallucinogens. These excellent contributions deal first with unconditioned and conditioned behaviours, ranging from studies of startle reflexes, locomotor behaviour and the '5-HT syndrome' through to schedule-controlled behaviour and the discriminative stimulus effects of hallucinogens. The articles emphasize the contribution that behavioural studies have made to understanding mode of action at the receptor level and there is a substantial measure of agreement implicating 5-hydroxytryptamine mechanisms, although it seems equally obvious that other transmitter systems must also be involved. Whether the same mechanisms can also account for the effects of phencyclidine and related compounds as well as for those of the indolealkylamines seems rather unlikely.

Hamon discusses the effects of hallucinogens on the metabolism and function of classical CNS transmitters, mainly monoaminergic systems, and reports on binding studies with hallucinogens as ligands. There is a surprising lack of information about any possible actions of hallucinogens on peptide and amino acid neurotransmitters. A short article by Aghajanian describes recent experiments beginning the analysis of hallucinogenic drug action with intracellular recording techniques. The background of work with extracellular recording is covered by Jacobs, who integrates results from electrophysiological and behavioural studies to argue strongly in support of a postsynaptic mechanism of action of hallucinogens at certain 5-hydroxytryptamine receptors. The book concludes with an imaginative contribution from Freedman, whose wide-ranging vision will doubtless help to attract researchers to this area. One wishes, however, that his discussion had attempted to integrate rather more of the recent work described in the earlier chapters, as the heading 'synthesis' above the article leads the reader to expect. It is also very obvious that while research in animals has been proceeding well, further progress is likely to be greatly impaired by the small amount of work carried out in human subjects over the last fifteen years. More human research appears to be urgently needed to validate the conclusions being reached in the animal studies and to stimulate their further development.

Overall, the book can be highly recommended to anyone who needs to obtain an overview of present knowledge about how hallucinogens work. The editor must be commended on bringing together such a fine collection of articles.

I. P. Stolerman

Neuronal and Extraneuronal Events in Autonomic Pharmacology. Edited by William W. Fleming, S. Z. Langer, Karl-Heinz Graefe and Norman Weiner. 1984. Pp. 280 New York: Raven Press. Price $62.50.

The title of this volume is perhaps a little misleading suggesting, as it may, a range of subject matter almost wide enough for a textbook on autonomic pharmacology. It is in fact a collection of 23 papers presented at a symposium held in June 1983 to celebrate the sixtieth birthday of U. G. Trendelenburg. All the participants were his former students, fellows and coworkers. The worth of such a compilation hinges on the standing and interests of the guest of honour, and it is not surprising then that in this instance the outcome is an unqualified success.

The first 8 papers deal in detail with the molecular and cellular mechanisms of the synthesis (and its control by tyrosine hydroxylase), uptake, storage, release and inactivation of catecholamines in adrenergic neurons and chromaffin tissue. The value of cell lines (particularly PC-12) for such work is made evident. Next comes an excellent section on the extraneuronal uptake and metabolism of catecholamines. A group of 5 papers is introduced by a first-rate survey by Trendelenburg himself. There then follow accounts of the applicability of his 'pump and enzyme' model for extraneuronal uptake to rat heart and dog saphenous vein. Two very good papers on uptake in tracheal and other smooth muscle conclude this section. The third part is on receptors, and comprises papers on the stereochemistry of adrenoceptor agonists, the role of α_2-receptors in the action of the tricyclic antidepressants, and the classification of the adenosine receptors on autonomic nerve endings. This article (by D. M. Paton and D. R. Webster) contains a useful account of the relationship between the various subclassification schemes (P_1–P_2; R, P; A_1, A_2) which coexist uneasily in the literature

The final group of papers begins with receptor activation and the events that follow therefrom. An admirable review by Fleming deals with changes in postsynaptic sensitivity in cardiac muscle. It will be salutary reading for anyone still inclined to think that a change in receptor number is the only important factor in either denervation- or reserpine-induced supersensitivity. This is followed by Endoh and Blinks's account of the effects of endogenous transmitters on calcium transients in mammalian atrial muscle. Their paper is a model of careful analysis.

Following the same logical progression, attention shifts to the whole organism, with papers on the effects of caffeine, exercise and noradrenaline on conscious macaques, and on cardiovascular changes in humans undergoing surgery. One learns here that most of the physiological alarms in the operating room are turned off, because they prove to be unhelpful! Finally, a delightful note by Kottegoda describes the unravelling of the cause of symptoms seen when tuberculosis patients in Sri Lanka consumed not quite fresh skipjacks (a local fish) The patients were on isoniazid, a potent diamine oxidase inhibitor, and the skipjacks turned out to contain unprecedented amounts of histamine . . .

Though the coverage is inevitably uneven because of the book's derivation there is not a single dull paper. The editors are to be congratulated on the quality of the work, and on the speed of its publication. What a pity it is so expensive.

D. H. Jenkinson

Immunocytochemistry. Edited by A. C. Cuello. IBRO Handbook Series: Methods in the Neurosciences Volume 3. 1983. Pp. 501. Chichester: John Wiley. Price £19.95 (soft cover).

The last decade has seen the successful application of immunological methods to the study of the nervous system—immunoassay to detect and measure brain antigens and immunocytochemistry to localize them in tissue sections. Great advances have also been made in the identification of neural cells in culture using monoclonal antibody. These methods are especially useful in the nervous system, because of the diversity of the cell population and complexity of the neuronal interconnections. There is therefore an increasing demand for information on immunological techniques as applied to neurobiology.

This volume, by a number of experts in the field, sets out to satisfy this need in the form of a handbook of immunocytochemical methods for use in the laboratory. Although primarily a practical manual, outlining a wide range of established and specialized methods, the theoretical background is not entirely neglected. The principles underlying the methods are considered in some detail and their limitations are outlined. The book gets off to a rather shaky start with a laboured and not very helpful discussion on immunological specificity, but soon gets into its stride with admirable chapters on immunofluorescence microscopy and immunoperoxidase techniques. These are followed by sections on double-labelling, autoradiography, monoclonal antibodies and the application of immunohistochemical methods to electron microscopy. The remaining chapters, more than half the book, deal with the neurobiological applications. There are sections on the identification of neural cells in culture and the staining of whole mounts, and a number of chapters on the immunohistochemistry of neurotransmitters and transmitter-related enzymes. These deal critically with the theoretical aspects as well as the practical details and most contain an appendix on materials and methods and an extensive list of references.

It is possible that some readers who look to the book for practical guidance may be put off by the somewhat theoretical approach—this is not a simple laboratory cook book. However, those that persist will be rewarded by a critical account of the methods used by experienced workers in the field. Its use as a laboratory handbook is also facilitated by the fact that the methods section in each chapter is clearly separated from the theoretical discussion. The best feature of this volume, reflecting the specialized interests of the editor, is the section devoted to neurotransmitters. These chapters are excellent, but some may feel that the disproportionate space devoted to this topic makes the book slightly less valuable than it might have been. Readers with an interest in the myelin antigens, for example, or brain-specific intermediate filaments, may be disappointed and there is little of interest to the practising neuropathologist. However, the book is a valuable addition to the literature on immunocytochemistry as applied to neurobiology. It is well printed and clearly illustrated. As befits a laboratory manual it is sturdily bound, and at £19.95 the price is reasonable.

S. Leibowitz

Cerebral Cortex. Volume 1. **Cellular Components of the Cerebral Cortex.** Edited by A. Peters and E. G. Jones. 1984. Pp. 565. London and New York: Plenum Press. Price $69.50.

There has been an explosive increase over the last decade in what we know about nonpyramidal cells in the cerebral cortex. What once we saw as a meaninglessly and only mildly heterogeneous collection of cells, characterized chiefly by negative features with respect to pyramidal cells, now stands revealed as a remarkably diverse collection of cell types with distinctive distributions and somal and dendritic morphologies, with specific axonal patterns and with specific (putative) transmitter characteristics. These advances reflect the research efforts of some of the very best contemporary neuroanatomists, conspicuous among whom are the editors and their colleagues, and the application of a number of new and not so new techniques, used alone or in various combinations (electron microscopy; Golgi impregnation; experimental degeneration; HRP tracing; immunocytochemistry and other techniques for transmitter-specific cell and terminal labelling). And although much of the new fine detail thus revealed has yet to be matched by or integrated with knowledge about local synaptic circuits, about overall patterns of input/output organization or about cortical physiology, our increased understanding of the anatomy of nonpyramidal cells is undoubtedly significant and should be a major impetus to continued and renewed efforts in this and related areas of research.

Although this volume touches upon several other aspects of cortical anatomy, its major thrust and contribution is to catalogue, occasionally repetitively, but invariably in meticulous and lavishly illustrated detail, these advances in our knowledge of the nonpyramidal cell populations. The editors introduce the topic with a history of anatomical studies and an overview of the categories of cortical neurons: A. Fairen, J. DeFelipe and J. Regidor provide a general survey of nonpyramidal cells based chiefly on Golgi preparations; J. S. Lund deals with spiny stellate cells, E. G. Jones and S. Hendry with basket cells, P. Somogyi and A. Cowey with double bouquet cells, A. Peters with both chandelier cells and bipolar cells, E. G. Jones with spiderweb cells, and A. Peters and R. L. Saint Marie with the axonal plexuses of smooth and sparsely spinous nonpyramidal cells.

There is also an exhausting account of the morphology, fine structure and development of pyramidal cells by M. Feldman, and two chapters on cytoarchitectonics which fit somewhat uncomfortably, both with one another and with the rest of the book. One is a relatively brief consideration of the principles of cytoarchitectonics by T. L. Kemper and A. M. Galaburda (23 pages) the other a lengthy treatise (almost 50 pages) on pigmentoarchitectonics, based on staining for the presence of lipofuscin pigment, by H. Braak. In the last three chapters of the book the emphasis switches from cell types to aspects of laminar organization: M. Marin Padilla provides a Golgi-based analysis of the structure and development of layer I, T. Tömböl an account of layer VI (again based chiefly on Golgi preparations) and E. G. Jones surveys the laminar organization of pyramidal cells in relation to the destinations of their axonal projections.

Given the breadth of coverage implied by the title of the book, some will perhaps feel that in their choice of subject matter and contributors the editors have been somewhat neglectful of nonmammalian vertebrates and of phylogenetically older parts of the mammalian cerebral cortex; and that the star billing accorded to the neocortical nonpyramidal cells results in insufficient emphasis being given to other aspects of (neo)cortical anatomy. It remains to be seen to what extent future volumes serve to redress these imbalances, but in any case, to complain, for example, that allocortex is under-represented in this book is to miss the point: it is mammalian visual and somatosensory cortices that have provided most of the new insights recounted here and it is almost inevitable for this reason—and for other reasons too—that there should be an overwhelming emphasis on neocortex.

Finally, it should be said that this is a very carefully edited and well-produced book, and for what it offers, very reasonably priced. The literary style, the organization of the individual chapters and the referencing are uniform, the type face and general layout attractive, the numerous illustrations superbly reproduced and the entire book printed on paper of the highest quality. This book was a pleasure to review. It is and will remain an indispensable reference source until it is replaced, as in due course it certainly must be, by the second edition. At the present rate of progress in the field, one can expect that a new edition will be needed well within ten years and one hopes that as soon as the other volumes of the series have been steered through to publication, the editors will put the matter in hand.

A. R. LIEBERMAN

FORTHCOMING EVENTS

Third International Brain Heart Conference

This Conference will be held in Trier, FRG, on September 7–9, 1985 as a satellite symposium to the Thirteenth World Congress of Neurology to be held in Hamburg on September 1–6, 1985. The scientific programme will include the following topics: central cardiovascular control; anatomical aspects of central nervous cardiovascular regulation; reflex control of circulation; neurochemical basis for cardiovascular control; central neural control of the systemic and cerebral circulations; central neurochemical alterations in hypertension; drugs controlling central blood pressure mechanisms; heart failure and neural control; neural control of the heart in arrhythmias.

Further information may be obtained from Dr T. Stober, Department of Neurology, Faculty of Medicine, University of Saarland, D-6650 Homburg/Saar, FRG.

Tenth International Congress of Neuropathology

The Tenth International Congress of Neuropathology will be held in Stockholm, Sweden, on September 7–12, 1986. There will be four major symposia: pathobiology of the axon; neurotransmitter and receptor systems in health and disease; energy crises in the brain, causes and consequences; viral infections. There will also be daily plenary sessions on important developments in neuropathology and neurobiology, slide seminars on muscle disease, intracranial tumours and tropical infections of the nervous system and, finally, free communications, workshops and poster sessions.

Further information may be obtained from the Tenth International Congress of Neuropathology, Stockholm Convention Bureau, PO Box 1617, S-111 86 Stockholm, Sweden.

Second International Headache Congress

This Congress, which is jointly sponsored by the International Headache Society and the Danish Migraine Society, will be held in the Hotal Scandinavia, Copenhagen, on June 18–21, 1985. The principal themes will be the physiology of head pain, clinical pharmacology and headache, psychological aspects of headache, classical migraine and clinical trials in migraine.

Information may be obtained from the Secretary, Second International Headache Congress, Department of Neuromedicine, Kobenhavns amts sygehus i Gentofte, 2900 Hellerup, Denmark.

American Association of Electromyography and Electrodiagnosis

The Thirty-second Annual General Meeting of the Association will be held at Caesar's Palace, Las Vegas, Nevada, on October 25–26, 1985. The deadline for receipt of abstracts for free communications is April 15, 1985. The Association is also sponsoring continuing medical educational courses and a Symposium on Peripheral Nerve Disease. Requests for information should be made to Ella M. VanLaningham, AAEE Executive Director, 732 Marquette Bank Building, Rochester, MN 55904.

Applications for the AAEE Young Investigator Award are also invited. These must be postmarked by April 15, 1985. The Award is open to residents or fellows in training and to electromyographers within two years following completion of the educational training required for AAEE active membership. It is given for original research in clinical neurophysiology and the paper must be submitted in a format suitable for publication. Applicants should submit 12 copies of the full manuscript, with abstract, accompanied by a letter from their Program Director attesting that they meet the qualifications. The winning paper will be submitted to *Muscle and Nerve* for first review and the abstract will be published in *Muscle and Nerve* and *EEG and Clinical Neurophysiology*. The winner will receive round trip transportation (within the domestic US), hotel accommodation, and a $200 cash award, and will present the paper at the AAEE Annual Meeting in Las Vegas, October 25-26, 1985. Papers should be submitted to Ella M. VanLaningham, AAEE Executive Director, address as above.

International Symposium on Molecular Aspects of Neurobiology

This symposium, sponsored by the Fondazione Giovanni Lorenzini, will be held in Florence, Italy, on June 19-21, 1985 and will be chaired by R. Levi Montalcini and E. R. Kandel. The provisional list of topics will include molecular aspects of growth factors, neuronal interaction and cell adhesion, cell surface receptor structure, neuronal cell lines, molecular properties of ion channels and pharmacological perspectives of molecular neurobiology.

Further information may be obtained from the Organizing Secretariat, Fondazione Giovanni Lorenzini, Via Monte Napoleone 23, 20121 Milano, Italy.

FYSSEN FOUNDATION

1985 International Prize

The Fyssen Foundation's general aim is 'to encourage all forms of scientific enquiry into cognitive mechanisms (including thought and reasoning), underlying animal and human behaviour, into their biological and cultural bases, and into their phylogenetic and ontogenetic development'. A substantial International Scientific Prize will be awarded for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, paleontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. It was awarded in 1980 to Professor André Leroi-Gourhan, in 1981 to Professor William H. Thorpe, in 1982 to Professor Vernon B. Mountcastle, in 1983 to Professor Harold C. Conklin and in 1984 to Professor Roger W. Brown.

The discipline for the 1985 Prize is Neuroscience. Nominations should include a curriculum vitae of the nominee, a list of his/her publications and a summary (four pages maximum) of the research upon which the nomination is based, and should be sent (15 copies) to the Secretariat of the Foundation, 194, rue de Rivoli, 75001 Paris. Self-nomination is not acceptable.

The final date for receipt of nominations is *September 1, 1985*.

Travel Grants For Young Neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
   (a) An abbreviated curriculum vitae and a list of any relevant publications;
   (b) Statement of age and post currently held;
   (c) A concise account of the purpose of the proposed visit;
   (d) A recommendation from the Head of Department (where appropriate);
   (e) A letter of acceptance from the Department to be visited;
   (f) A statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr. M.J.G. Harrison
Reta Lila Weston Institute of
Neurological Studies,
Middlesex Hospital Medical School,
London WIN 8AA

Reduced Subscription Rates

A reduced subscription rate (£20.00 per annum) is available to young subscribers under the age of 40 years, who are in a training post in clinical neurology or in the neurosciences in the UK. Applications for this special rate should be made to Dr M. J. G. Harrison, The Middlesex Hospital, Mortimer Street, London, W1N 8AA with a letter from the head of department confirming the applicant's eligibility.

ISSN 0006-8950

Brain

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A JOURNAL OF NEUROLOGY

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SOMATOSENSORY EVOKED POTENTIALS IN CERVICAL SPONDYLOSIS

CORRELATION OF MEDIAN, ULNAR AND POSTERIOR TIBIAL NERVE RESPONSES WITH CLINICAL AND RADIOLOGICAL FINDINGS

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SUMMARY

Somatosensory evoked potentials (SEPs) following median, ulnar and tibial nerve stimulation were recorded from sites over the shoulders, neck and scalp in 34 patients with cervical spondylosis. Twenty control subjects were matched for sex and age. Detailed clinical and radiological data were assembled, with particular attention to the sensory modalities impaired and the locus and severity of cord compression. The patients were divided clinically into 4 groups: combined myelopathy and radiculopathy (6 cases), myelopathy alone (15), radiculopathy (6) and neck pain (7). Four cases are described in detail.

SEP abnormalities were strongly correlated with clinical myelopathy, but not with radiculopathy. Median and ulnar nerve responses were less often affected than tibial, even with myelopathy above C6 level. Tibial nerve SEP abnormalities were strongly correlated with posterior column signs on the same side of the body, but not with anterolateral column sensory signs. In myelopathy cases, the SEP examination appeared to be more sensitive to sensory pathway involvement than clinical sensory testing. SEP abnormalities were infrequent in cases of radiculopathy and neck pain, bearing no relation to the clinical locus of root lesions. Abnormal SEPs consistent with subclinical posterior column involvement, however, were recorded in 1 patient with radiculopathy and 2 with neck pain. Follow-up recordings made postoperatively in 7 myelopathy cases reflected the clinical course (improvement, deterioration or no change) in 4, but failed to reflect improvement in 3.

The correlation of SEP findings with radiological data was generally poor. SEP abnormalities were detected in 6 out of 8 patients with clinical myelopathy but no radiological evidence of posterior cord compression, suggesting that impairment of the blood supply may be an important factor contributing to cord damage.

An application for SEPs in the clinical management of cervical spondylosis may lie in the detection of posterior column involvement and the differential diagnosis from disorders such as multiple sclerosis and amyotrophic lateral sclerosis.

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INTRODUCTION

The first somatosensory evoked potentials (SEPs) recorded from the scalp of a human subject were the pathologically enhanced responses of a patient with progressive myoclonic epilepsy (Dawson, 1947). With the development of signal averaging techniques (Dawson, 1954) it became possible to analyse the individual components of the normal waveform, and this capability has recently been extended to the sequence of short-latency potentials generated in the brachial plexus, spinal cord and subcortical structures (Cracco, 1973; Matthews *et al.*, 1974; Jones, 1977; Hume and Cant, 1978; Kritchevsky and Wiederholt, 1978; Desmedt and Cheron, 1980). The clinical application of the SEP technique has been investigated in a number of conditions affecting the proximal root segments and the spinal cord, including traumatic lesions (Jones, 1979) and multiple sclerosis (Small *et al.*, 1978; Eisen and Odusote, 1980).

Cervical spondylosis is a common condition after the age of 40 years (Irvine *et al.*, 1965). Cervical spondylotic myelopathy is considered to be the commonest cervical cord disorder during and after middle age (Wilkinson, 1960; Crandall and Gregorius, 1977), but cervical spondylotic radiculopathy is undoubtedly more prevalent. While the clinical picture of these conditions was clearly delineated more than three decades ago (Frykholm, 1951; Brain *et al.*, 1952), pathogenetic mechanisms have yet to be fully understood. Spondylotic protrusion alone is not an adequate explanation for the cord damage. Compared with the prevalence of cervical spondylosis, that for an associated myelopathy is small and there is surprisingly little correlation between the severity of radiological spondylosis and the presence or severity of myelopathy. Moreover, the diagnosis may still be uncertain at times. In one group of patients initially diagnosed as having spondylotic myelopathy, as many as 17 per cent were later shown to have other diseases such as multiple sclerosis (Campbell and Phillips, 1960). It follows, therefore, that radiological evidence of spondylosis may not be a sufficient explanation for neurological symptoms implicating the cervical spinal cord.

It is natural that the investigative utility of SEPs in this field should be explored, and there have already been a number of published investigations (Fukushima and Mayanagi, 1975; Matsukado *et al.*, 1976; Mastaglia *et al.*, 1978; El-Negamy and Sedgwick, 1979; Chiappa *et al.*, 1980; Ganes, 1980; Noël and Desmedt, 1980; Schramm, 1980; Siivola *et al.*, 1981). None of these, however, attempts a detailed comparison of electrophysiological findings with clinical and radiological data. Consequently, the clinical application of SEPs in cervical spondylosis has not so far been fully defined, and the present study was undertaken with this object in view.

PATIENTS AND METHODS

Thirty-four patients with symptomatic evidence of cervical spondylosis were studied, with informed consent, at the National Hospital, Queen Square, London, between September 1981 and October 1982. There were 20 males aged 44 to 74 years (mean 60 years) and 14 females aged 31 to 81 (mean 58 years).

The control group comprised 10 males and 10 females aged 47 to 83 (mean 63 years). These were volunteers who had no symptoms or signs referrable to cervical spondylosis or to any other disease involving the sensory pathway. The 2 youngest patients, aged 31 and 33, were compared with 29 controls aged 19 to 36 years.

Clinical Methods

All patients were examined personally at presentation and at subsequent visits. Clinical findings were classified according to the level of spinal cord involvement and particular tract dysfunction as follows. (1) Posterior column involvement was indicated by impairment of joint position and vibration sense. (2) Anterolateral column involvement was indicated by upper motor neuron signs, disturbance of bladder control or impairment of pain and temperature sensation. (3) Radicular involvement was indicated by segmental sensory disturbance, diminished tendon reflexes or weakness and wasting in the upper limbs. When associated with brisk upper limb reflexes, however, the last feature was taken to indicate anterior horn cell damage (electromyography was performed in 3 out of 7 of the latter and showed denervation changes in the relevant muscles. Nerve conduction was normal.)

Relevant investigations, including CSF analysis with estimation of IgG concentration and fractionation, visual and auditory evoked potentials, serum B_{12} and red cell folate levels and blood VDRL and TPHA tests were performed to exclude intrinsic cervical cord disease.

The patient's functional disability was graded as mild when daily activity was only slightly affected, moderate when there was dependence on aids or help, and severe when the patient was bedridden, chairbound or had useless upper extremities.

The clinical course after conservative or surgical treatment was assessed in all cases, with a mean follow-up period of nine months (SD 4.2, range 3–17 months). Clinical improvement was considered marked if the functional status had moved up one grade or more, and slight if there had been a less pronounced, although significant, decrease in the severity of symptoms and signs. Clinical deterioration was similarly assessed.

Radiological Methods

In all cases plain radiographs of the cervical spine were taken in lateral, anteroposterior, right and left oblique, flexion and extension views. A slab of perspex embedded with lead markers 1 cm apart was taped to the midline of the spine such that the true sagittal diameter of the cervical canal could be obtained after correction for the magnification factor in the film. The distance between the nearest points of the posterior margin of the vertebral body and the lamina at each intervertebral disc level was measured, and the narrowest defined as minimal sagittal diameter (mAPD). The degree of spondylosis was assessed according to changes of spine curvature, narrowing of disc spaces, anterior and posterior osteophytosis, encroachment of intervertebral foramina and subluxation, and the gradings of mild, moderate or severe spondylosis assigned.

During metrizamide myelography (performed in all cases with clinical evidence of myelopathy or radiculopathy), posteroanterior (PA), lateral, oblique, flexion and extension views were taken with the patient in the prone position. Cord compression was indicated by blockage of contrast flow, cord flattening in PA views and anterior or posterior cord indentation in lateral views. Root compression was shown as occlusion, distortion or displacement of the root pouches and sleeves. Postmyelography computed tomography (PMCT) was performed in 19 cases. This contributed the cross-sectional view and showed more clearly the site(s) of cord compression, whether anterior or posterior, bilateral or unilateral, central, lateral or diffuse. The degree of compression was also graded as mild, moderate or severe, and the worst grade shown in either of the two investigations was chosen.

Electrophysiological Methods

Electrical stimuli (square-wave constant current impulses of duration 0.2 or 0.5 ms) were delivered at 3/s to the median and ulnar nerves at either wrist, and the posterior tibial nerve at either ankle. The intensity was adjusted so as to produce a moderate twitch of the appropriate muscles. Following upper limb stimulation, SEPs were recorded with silver/silver chloride disc electrodes attached over the supraclavicular fossa, the Cv7 and Cv2 vertebrae and the hand area of the contralateral sensory cortex (7 cm lateral to a point 2 cm posterior to the vertex). Following lower limb stimulation the recording sites were over the midline foot area of the sensory cortex (2 cm posterior to the vertex) and the left and right hand areas. All electrodes were referred to a site on the midline 12 cm above the nasion (Fz, International 10–20 System). The amplifier high-frequency response was less than 3 dB down at 5 kHz and the time constant was 1 s. Groups of 200 or 400 responses were averaged, with a sweep duration of 32 ms (sampling rate 8 kHz) starting 3 ms after a stimulus to the upper limb, or of 64 ms (sampling rate 4 kHz) starting 13 ms after lower limb stimulation. Having examined repeat recordings for reproducibility, these were combined into grand average waveforms consisting of up to 1200 individual responses.

RESULTS

Classification of Patients

The patients were classified into 4 groups according to clinical features (*see* Tables 1 and 2).

(1) Combined myelopathy and radiculopathy, 6 cases. Symptomatic root and cord lesions were confirmed by plain radiographs and myelography in all cases, and by CT scanning (PMCT) in 3.

(2) Myelopathy alone, 15 cases. Cord involvement was confirmed by plain radiographs and myelography in all cases, and by PMCT in 12.

(3) Radiculopathy alone, 6 cases. Plain radiographs and myelography were performed in all cases, and PMCT in 4. This confirmed root lesions in all cases except 1.

(4) Neck pain, 7 cases. Sensory and motor signs were absent, although sometimes mild pain and/or paraesthesiae extended into the upper limbs. Plain radiographs provided evidence of degenerative changes in all cases.

Classification of SEP Abnormalities

The principal components examined were N9 (supraclavicular electrode), N13 (Cv7 or Cv2) and N20/P25 (hand area) following upper limb stimulation, and P40 (midline foot area) following stimulation of the lower limb. Components were named according to their polarity and mean peak latency in normal subjects. Normal ranges, including the limits of left/right variability, were derived for the amplitude and latency of each component plus intercomponent conduction times. Limits of normal latency were defined by the mean ± 2.5 standard deviations of the control group, male or female. Amplitude limits were defined by the absolute range of the control group with both sexes combined.

SEP abnormalities in the patient group were classified as follows (*see* Tables 1 and 2 and figs. 1–4).

(1) Abnormality of N9 (supraclavicular electrode) following median or ulnar nerve stimulation was taken to indicate a lesion at or distal to the dorsal root ganglia, C6 and/or C7 for the median nerve and C8 and/or T1 for the ulnar.

TABLE 1. CLINICAL, RADIOLOGICAL AND SEP FINDINGS IN CERVICAL SPONDYLOTIC MYELOPATHY WITH RADICULOPATHY AND MYELOPATHY ALONE

			Clinical findings						*Radiological findings*					*SEP findings*						
						Anterolat cols			*Plain x-rays*		*Myelogram/PMCT Cord compression*			*Median*		*Ulnar*		*Tibial*		
Case	*Sex*	*Age (yrs)*	*Duration (mo) disability*	*Cord level*	*Post cols*	*Motor*	*Sensory*	*Roots*	*mAPD (mm)*	*CS*	*Level*	*Ant*	*Post.*	*L*	*R*	*L*	*R*	*L*	*R*	*Treatment/response*
Myelopathy plus radiculopathy																				
1	F	78	5/++	> C5	L+R	L+R	L+R	R C5, 6	10.5	+++ C4/5 S	C4/5 5/6	+++ ++	+++ ++	N	N	SC	SC	SC	SC	Conservative/nil
2	M	51	10/+	C5	N	L+R	N	R C6, 7, 8	12.7	++	C5/6 6/7	++ +		N	N	N	N	N	N	Conservative/++
3	M	65	60/++	C5	N	L+R	N	L C6, 7, 8 R C6	9.0	+++	C3/4 6/7	+++ +++	++ ++	N	N	DI	PR	SC	N	Conservative/nil
4	M	71	12/++	C7	N	L+R	L	L C5, 6, 7 R C5, 6, 7	10.5	++	C4/5, 5/6 (L C6, R C5, 6 roots)	+		N	N	N	DI	N	N	Conservative/nil
5	M	61	36/++	C5	L+R	L+R	L+R	L C5, 6 R C5, 6	LAM	++	C4/5	LAM	LAM	PR	PR	PR	PR	SC	SC	Conservative/nil
6	M	74	48/+++	> C5	N	L+R	N	R C5, 6	LAM	++	C3/4, 4/5, 5/6 (L, R C5, 6 roots)	LAM	LAM	PR	NA	SC	NA	SC	SC	Conservative/nil
Myelopathy alone																				
7	M	59	60/+	C5	L	L+R	R	None	11.5	++	C4/5 5/6, 6/7	++ +		N	N	N	N	N	N	C4/5, 5/6, 6/7 Cloward/nil
8	M	57	6/++	> C5	R	L+R	L+R	None	10.0	++	C5/6	++	++	N	N	N	N	N	SC	C5/6 anterior discotomy/++
9	M	52	6/++	> C5	L+R	L+R	R	None	11.0	+	C3/4 (R C6 root)	+		N	N	SC	N	SC	SC	C2–7 laminectomy/++
10	F	43	2/++	> C5	L+R	L+R	L+R	None	10.5	++	C5/6 6/7	+++ +	+++	N	N	N	N	SC	SC	C5/6, 6/7 Cloward/++
11	M	52	18/++	> C5	N	L+R	N	None	10.0	+++	C4/5 3/4, 5/6	++ +	++	N	N	N	PR	N	N	C5–7 laminectomy/++
12	M	71	36/+++	> C5	L+R	L+R	N	None	13.0	++	C4/5 6/7	+++ ++	+++	SC	PR	N	DI	N	SC	C4/5 Cloward/++
13	M	52	48/++	> C5	L+R	L+R	L+R	None	10.0	++ C3/4 S	C3/4	++	++	N	N	N	N	N	N	C3/4 Cloward/–
14	F	46	12/+	> C5	N	L+R	L+R	None	14.0	+	C3/4	+		N	N	N	PR	SC	N	Conservative/nil
15	F	52	12/++	> C5	N	L+R	N	None	9.6	++ C5/6 S	C5/6	++	++	N	N	N	N	N	SC	Conservative/nil
16	F	63	144/+++	> C5	L+R	L+R	L+R	None	11.7	+++ C4/5 S	C3/4, 4/5 5/6 (L C6 root)	+++ ++	+++	N	PR	PR	PR	SC	SC	Conservative/nil
17	M	65	12/++	> C5	L+R	L+R	L+R	None	11.8	++ C3/4 S	C3/4 (L, R C5 roots)	++		PR	PR	DI	SC	SC	SC	C3/4 Cloward/+
18	M	59	9/++	> C5	L+R	L+R	L+R	None	10.5	++ C5/6 S	C3/4 4/5, 5/6	++ ++	+	N	N	N	PR	N	SC	Conservative/–
19	F	81	84/+++	T1	L+R	L+R	L+R	None	11.0	+++	C4/5, 5/6	++		N	N	N	N	SC	SC	Conservative/nil
20	F	57	84/++	> C5	L	L+R	N	None	LAM	+++	C4/5	LAM	LAM	N	N	N	N	SC	N	Conservative/nil
21	F	31	15/++	C5	N	L+R	R	None	11.7	+	C5/6	+		N	N	N	N	N	SC	C5/6 Cloward/++

mAPD and the degree of cord compression were not recorded in 3 cases (5, 6, 20) with previous posterior laminectomy PMCT was not performed in 6 cases ((3, 5, 6, 7, 15, 19)

Abbreviations used in Tables 1, 2 and 3 M = male, F = female, L = left, R = right, N = normal, NA = not assessed, CS = cervical spondylosis, S = subluxation, > = above; DI = distal or ganglionic lesion, PR = proximal root/cord lesion; SC = spinal cord lesion, LS = lumbosacral root lesion, LAM = previous posterior laminectomy, + = mild degree (or slight improvement after treatment), ++ = moderate degree (or marked improvement), +++ = severe degree, – = slight deterioration.

(2) Abnormality of N13 (Cv7 or Cv2) with normal N9 was taken to indicate a lesion proximal to the dorsal root ganglia, involving root fibres or the spinal cord. It was noted, however, that increased N9–N13 conduction time without attenuation of N13 might be due to delayed conduction proximal to the clavicular electrode but just distal to the dorsal root ganglia.

(3) Abnormality of N20/P25 (hand area) with normal N9 and N13 was taken to indicate a spinal cord lesion. No significant dissociation was noted between N13 recorded at Cv7 and the similar potential recorded at Cv2.

(4) Abnormality of P40 (midline foot area) was taken to indicate a spinal cord lesion. This interpretation was rejected, however, in one patient in the radiculopathy group who had a long history of sciatica on the appropriate side.

Incidence of SEP Abnormalities and Correlation with Patient Classification

In the patient group as a whole, abnormality of at least one SEP was detected in 22 cases out of 34 (i.e. 65 %). For the 3 nerves tested the percentage incidences were median 18, ulnar 41 and tibial 56. Abnormality of at least one SEP was detected in 5/6 cases with combined myelopathy and radiculopathy (83 %), 13/15 with myelopathy alone (87 %), 2/6 with radiculopathy alone (33 %) and 2/7 with neck pain (29 %). Abnormality of at least 4 SEP recordings was seen in 3 cases of combined myelopathy and radiculopathy (50 %), 3 of myelopathy (20 %) and none of the other two groups. There was, therefore, a significant correlation of SEP abnormality with myelopathy ($P < 0.01$, χ^2 test), but not with radiculopathy. Abnormality of the tibial nerve SEP was correlated with myelopathy ($P < 0.02$) but not with radiculopathy,

TABLE 2. CLINICAL, RADIOLOGICAL AND SEP FINDINGS IN CERVICAL SPONDYLOTIC RADICULOPATHY AND NECK PAIN

			Clinical findings		*Radiological findings*			*SEP findings*						
					Plain x-rays			*Median*		*Ulnar*		*Tibial*		
Case	*Sex*	*Age (yrs)*	*Duration (mo) disability*	*Roots*	*mAPD (mm)*	*CS*	*Myelogram/PMCT Roots*	*L*	*R*	*L*	*R*	*L*	*R*	*Treatment/response*
Radiculopathy														
22	M	44	1/+ +	L C5, 6	14.5	+	L C6	N	N	N	DI	LS	N	Conservative/+ +
23	M	48	24/+ +	L C7/8	12.3	+	L C7, R C6, 7 (C5/6 ant +)	N	N	N	N	N	N	Conservative/nil
24	F	33	2/+ +	L C5, 6	14.0	+	N	N	N	N	N	N	SC	Conservative/+ +
25	F	64	1/+ + +	L C5, 6	13.0	+ +	L C5, 6	N	N	N	N	N	N	C4/5, 5/6 facetotomy/+ +
26	F	71	72/+	R C5, 6	13.0	+ +	L C6, R C6 (C3/4, 6/7 ant post +)	N	N	N	N	N	N	Conservative/+ +
27	F	58	3/+ + +	L C7, 8	11.0	+ + +	L C6, 7, R C5, 6 (C4/5 ant + + post + C5/6, 6/7 ant +)	N	N	N	N	N	N	C4–7 laminectomy, C6/7 facetotomy/nil
Neck pain														
28	M	59	24/+	None	14.0	+	NA	N	N	DI	PR	N	N	Conservative/+ +
29	F	72	60/+	None	13.0	+ +	NA	N	N	N	N	N	N	Conservative/+ +
30	M	64	12/+	None	12.0	+ +	NA	N	N	N	N	N	N	Conservative/+ +
31	M	68	60/+	None	13.0	+ +	NA	N	N	N	N	N	N	Conservative/+ +
32	M	69	24/+	None	12.0	+ + C3/4 S	NA	N	N	N	N	N	N	Conservative/+ +
33	F	61	48/+ +	None	15.0	+	NA	N	N	N	N	N	N	Conservative/+
34	M	66	36/+ +	None	15.5	+ +	NA	N	PR	N	N	SC	SC	Conservative/nil

PMCT was not performed in 2 cases (22, 25) of the radiculopathy group

[*Text continues on page 284*]

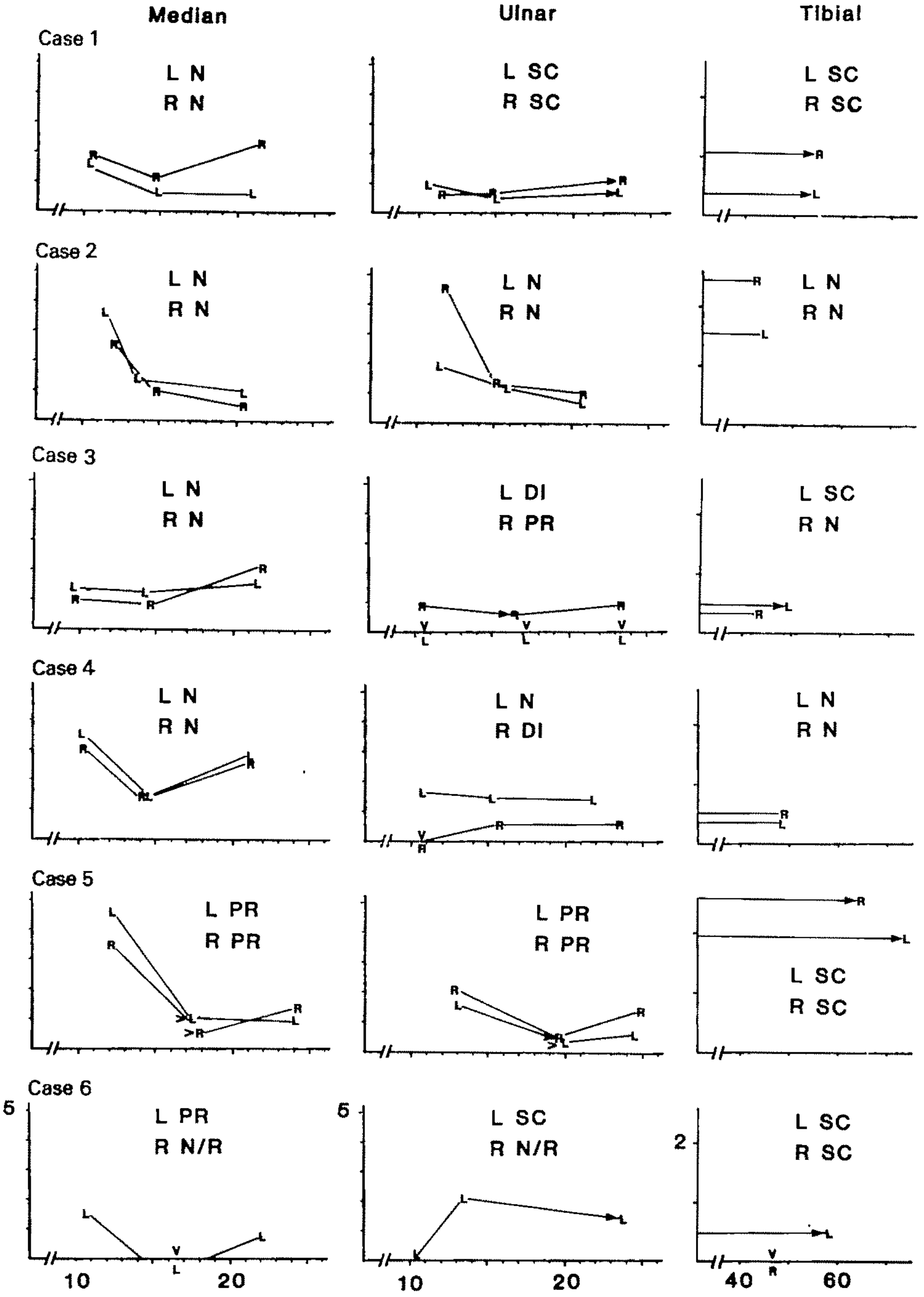


FIG. 1 SEP amplitude and latency values for each patient of the myelopathy plus radiculopathy group. The vertical axes are calibrated in μV and the horizontal in ms. For median and ulnar nerve responses, the three connected points denote N9, N13 and N20 from the left (L) and right (R) arms. For tibial nerve responses the points denote P40, left and right. Low amplitude or absent components are indicated by ' v ', and the earliest components with prolonged latency by '>' SEPs deviating significantly from normal (N) were classified as suggesting distal (DI), proximal (PR) or spinal cord (SC) defects. For Case 6, the right arm could not be accessed at the wrist.

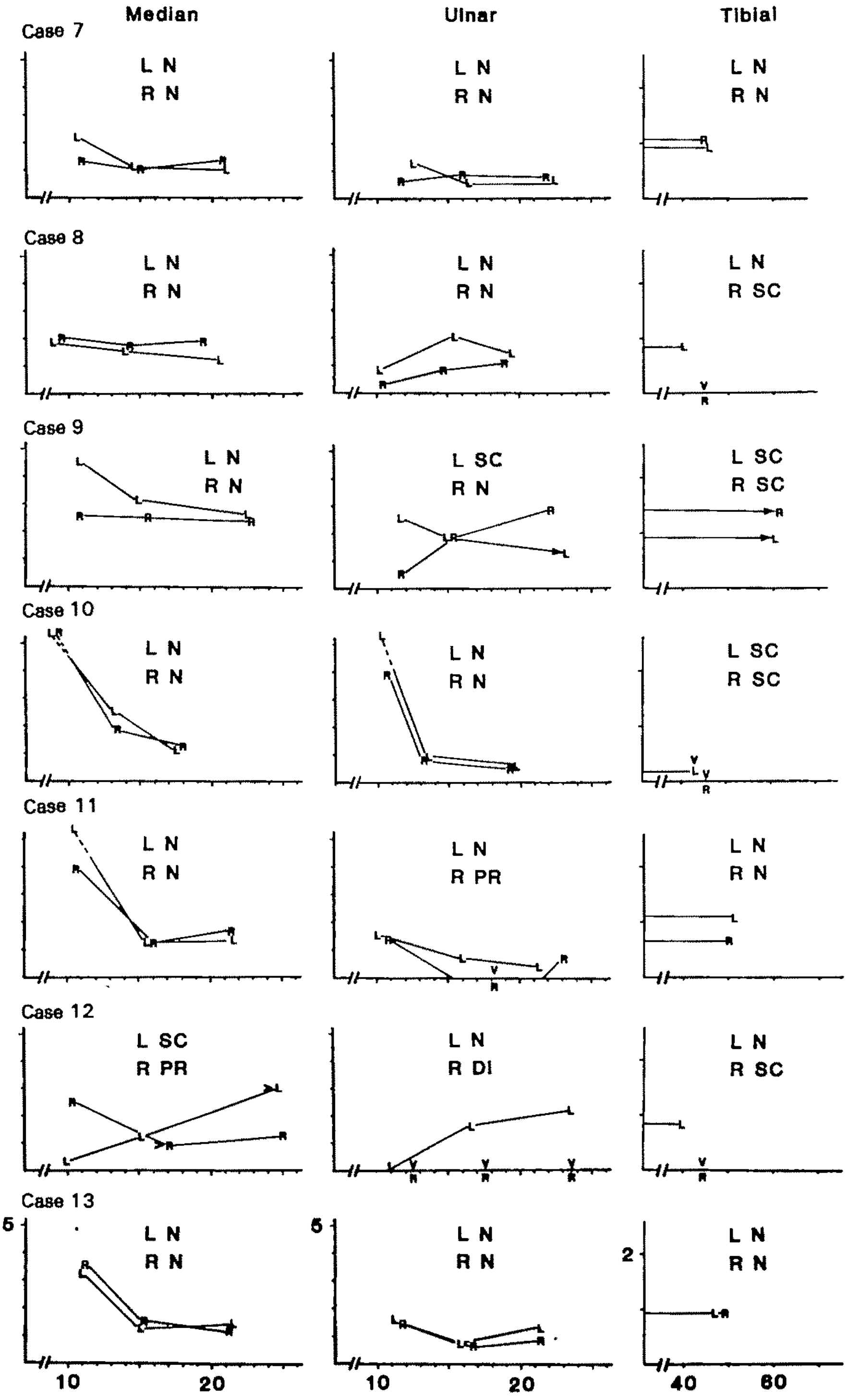
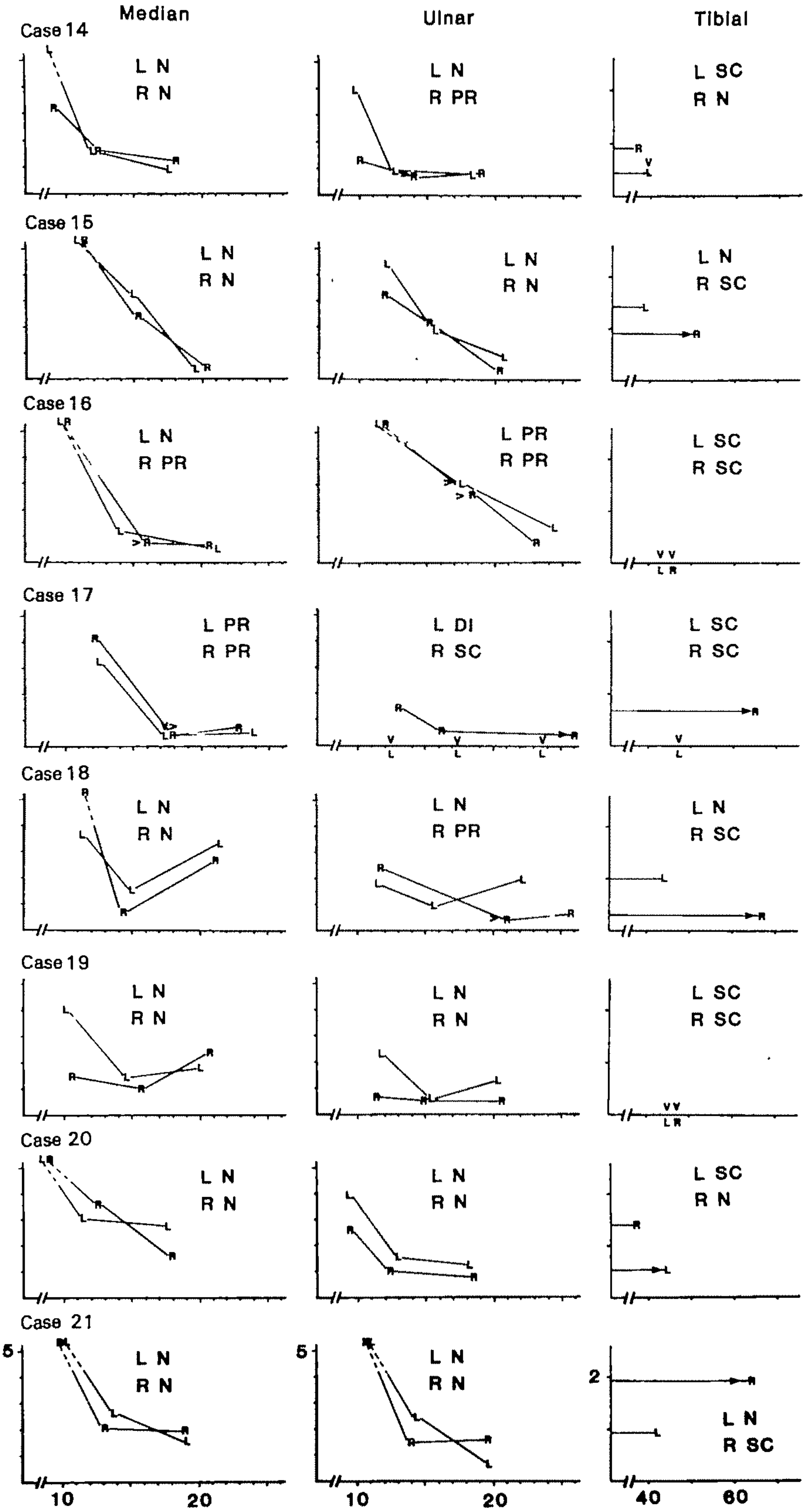


FIG. 2. SEP amplitude and latency values for each patient of the myelopathy group. For explanation of abbreviations, *see* legend for fig. 1. Dashed lines indicate components of large amplitude, beyond the limit of the vertical axis.


Median
Ulnar
Tibial
Case 14
L N
R N
L N
R PR
L SC
R N
Case 15
L N
R N
L N
R N
L N
R SC
Case 16
L N
R PR
L PR
R PR
L SC
R SC
Case 17
L PR
R PR
L DI
R SC
L SC
R SC
Case 18
L N
R N
L N
R PR
L N
R SC
Case 19
L N
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L N
R N
L SC
R SC
Case 20
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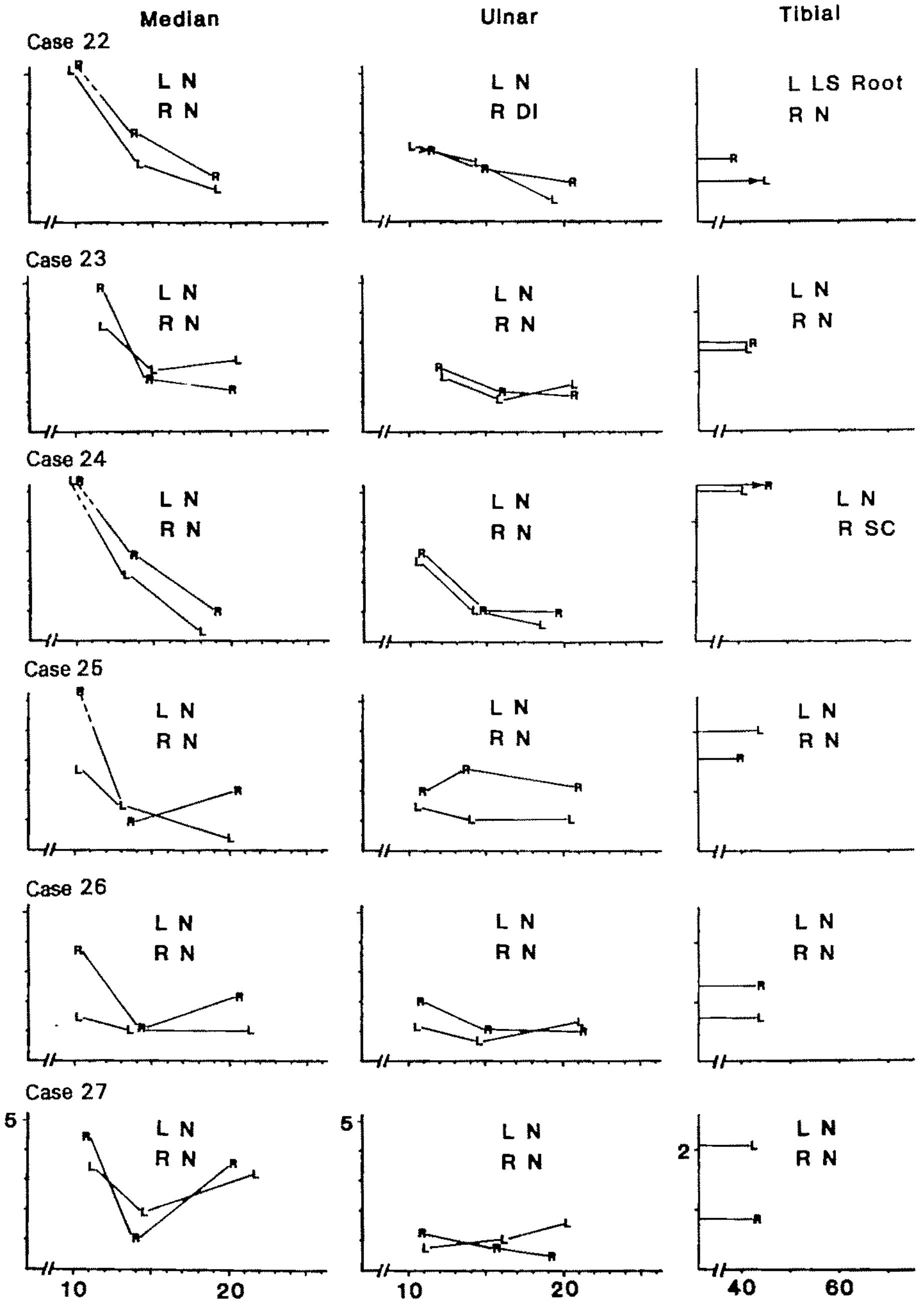

FIG. 3. SEP amplitude and latency values for each patient of the radiculopathy group. For explanation of abbreviations and dashed lines, *see* legends for figs. 1 and 2. For Case 22, the delayed left tibial nerve response was ascribed to an established lesion of the lumbosacral roots on this side.

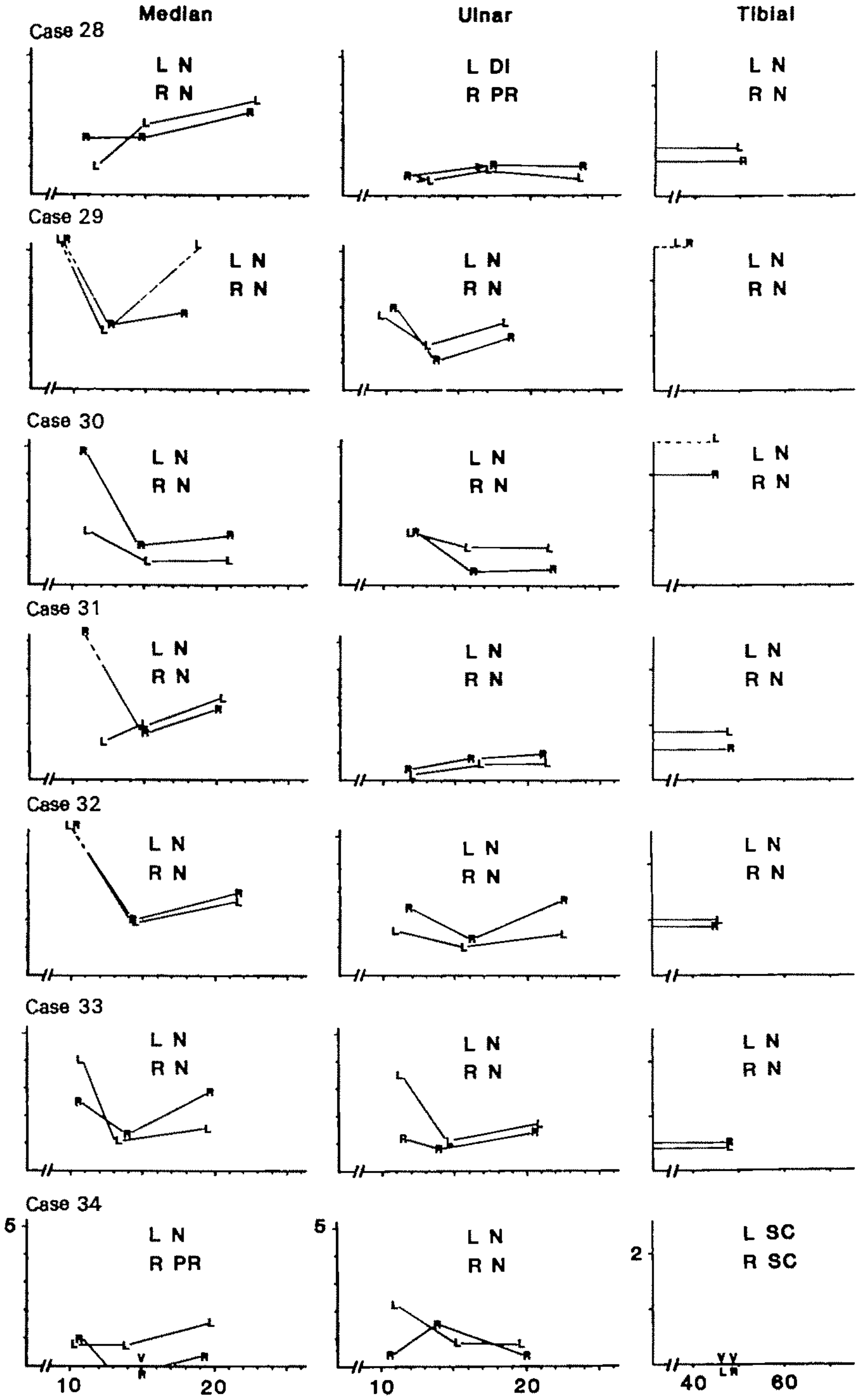

FIG. 4. SEP amplitude and latency values for each patient of the neck pain group For explanation of abbreviations and dashed lines, *see* legends for figs. 1 and 2.

whereas upper limb SEP abnormalities were correlated with neither pathology. The lack of correlation with radiculopathy was particularly apparent when upper limb SEP abnormalities were compared with the clinical loci of root lesions (*see* Radiculopathy section below), and therefore it was considered justifiable to combine the myelopathy-with-radiculopathy and isolated myelopathy groups in order to examine the correlation of SEP abnormalities with myelopathy.

Myelopathy

In the cases of myelopathy, with and without radiculopathy (Table 1, figs. 1 and 2), SEP abnormalities were detected in 18 out of 21 patients (86%); 76 per cent of patients had abnormal tibial nerve responses, 57 per cent ulnar and 24 per cent median. Out of 5 patients with normal tibial nerve responses, 2 had an abnormal ulnar SEP on one side. In one of these, however, the pattern was that of a distal or ganglionic lesion, with no evidence of spinal cord involvement. Clinical examination revealed abnormal sensory signs in 16 (76%), suggestive of posterior column involvement in 13 (62%) and anterolateral column involvement in 14 (67%). Abnormality of the tibial nerve SEP was significantly correlated with posterior column signs on the same side of the body ($P < 0.01$), but not with anterolateral column signs ($P > 0.05$). Out of 8 patients without posterior column signs, however, 4 had unilateral and 1 bilateral tibial nerve SEP abnormalities. Out of 5 patients with normal tibial nerve SEPs, posterior column signs were present unilaterally in 1 and bilaterally in 1. Assuming that abnormality of the tibial nerve SEP reflects posterior column involvement, the SEP examination was thus marginally more sensitive than clinical sensory testing. No significant correlation was demonstrated between median or ulnar nerve SEPs and clinical signs of posterior or anterolateral column involvement.

Out of the 18 cases of myelopathy with abnormal SEPs, the clinical level of myelopathy was at or above C5 in 16, at C7 in one (with a 'distal' abnormality of one ulnar SEP only) and at T1 in the last. Radiological evidence (myelography and PMCT) suggested a level at or above C5/6 in all 18. This did not agree with the level of the lesion suggested by SEP findings, which was at or above C6 in only 5 cases (with abnormal median nerve SEPs), between C6 and C8 in 7 (with normal median and abnormal ulnar nerve responses) and below C8 in 6 (with normal median and ulnar but abnormal tibial nerve responses). A possible explanation for this anomaly is considered in the Discussion. Functional disability was judged to be severe in 4 patients, all with abnormal SEPs. Disability was mild in 3 patients, 2 having normal SEPs. The mean duration of symptoms, however, was not significantly different in patients with and without SEP abnormalities.

In the plain radiographs, 18 out of 21 patients with myelopathy had moderate to severe degenerative changes and 3 had mild changes. Subluxation was present in 6 patients. Foraminal encroachment (not tabulated as an individual parameter on account of the frequent multiplicity of locations) was judged to be mild to moderate in 10 cases and severe in 2. Minimal sagittal diameter (excluding 3 patients with previous posterior laminectomy) was normal in 9 cases, abnormal in 5 and borderline (10.5 mm) in 4. None of these measures was significantly correlated with SEP abnormalities. Excluding the same 3 patients with previous posterior laminectomy, the presence and degree of cord compression was assessed in myelography, with or without PMCT. SEPs were abnormal in 8 out of 9 cases with moderate or severe posterior compression, but also in 6 out of 8 for whom no posterior compression was apparent. All 5 patients with severe anterior compression had abnormal SEPs, compared with 10 out of 13 with mild or moderate anterior compression.

Twelve patients were managed conservatively with cervical collars and physiotherapy. Nine were treated surgically, 7 by the anterior approach (Cloward procedure 6, discotomy 1) and 2 by posterior laminectomy. Operative findings generally confirmed the location of cord compression indicated by radiology. The mean follow-up period was 9.7 months (SD 3.8 months). Of those treated conservatively, 1 showed marked clinical improvement, 1 slight deterioration and 10 no change. In the operated group, 6 showed marked improvement, 1 slight improvement, 1 slight deterioration and 1 no change. There was, therefore, a significantly better outcome in the operated group ($P < 0.01$, two-tailed). In neither group, however, was the outcome significantly predicted by normality or abnormality of the preoperative SEPs.

Repeat SEP recordings were made in 7 operated patients, three to six months after surgery (*see* Table 3). Clinically, 5 of these showed marked improvement, 1 mild deterioration and 1 no change. One patient with normal preoperative SEPs (Case 7) showed no clinical improvement, and no change in the SEP. Three patients with initially abnormal right tibial, left and right tibial plus left ulnar, and right ulnar nerve SEPs (Cases 8, 9 and 11, respectively) showed marked clinical improvement, but with no corresponding SEP change. In one patient with initially abnormal tibial nerve SEPs (Case 10, *see below*), marked clinical improvement was accompanied by

TABLE 3 POSTOPERATIVE SEP CHANGES IN 7 CASES OF CERVICAL SPONDYLOTIC MYELOPATHY AND 1 OF RADICULOPATHY

		Median		*Ulnar*		*Tibial*	
Case	*Clinical response*	*L*	*R*	*L*	*R*	*L*	*R*
Myelopathy							
7	Nil	Nil	Nil	Nil	Nil	Nil	Nil
8	++	Nil	Nil	Nil	Nil	Nil	Nil
9	++	Nil	Nil	Nil	Nil	Nil	Nil
10	++	Nil	Nil	Nil	Nil	++	++
11	++	Nil	Nil	Nil	Nil	Nil	Nil
12	++	+	+	Nil	Nil	Nil	Nil
13	−	−	Nil	−	−	−	−
Radiculopathy							
27	Nil	Nil	Nil	Nil	+	Nil	Nil

corresponding improvement of both tibial nerve SEPs. In another (Case 12) initially abnormal median nerve responses improved slightly in association with considerable clinical improvement, but abnormal right ulnar and tibial nerve responses were unchanged. One patient with initially normal SEPs (Case 13, *see below*) showed a slight deterioration of all except the right median nerve response, in keeping with slight clinical deterioration. There was, therefore, some agreement between clinical and electrophysiological changes in 4 out of 7 cases.

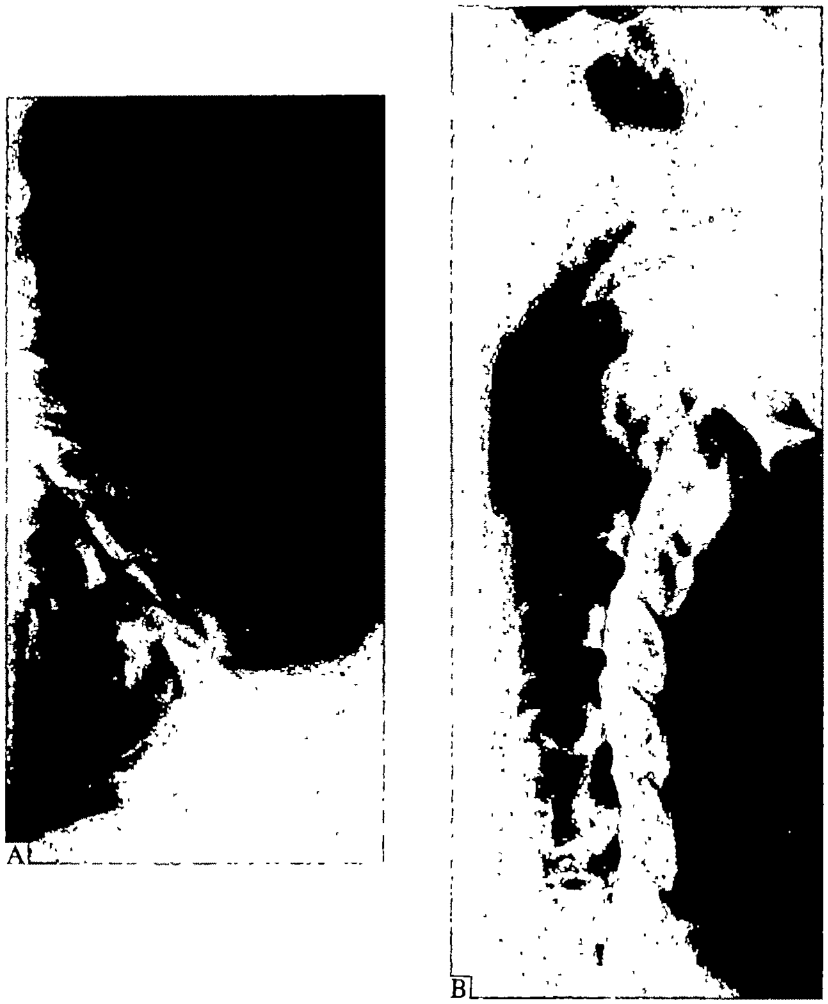

FIG. 5. Preoperative (A) and postoperative (B) myelograms of Case 10 (cervical spondylotic myelopathy) taken in lateral view. Marked anterior and posterior cord indentation at C5/6 seen in the preoperative picture (arrows) was largely relieved following the Cloward procedure

Illustrative Cases: Myelopathy

Case 10 (myelopathy alone), a female book-keeper, aged 43 years, developed paraesthesiae and numbness in the fingers of both hands two months before admission, with deterioration of grip and dexterity. At the same time her legs became clumsy, resulting in a single fall. There was no history of neck pain or injury, nor of sphincter disturbance.

Examination revealed a full range of neck movements without pain. The cranial nerves were normal. There was a mild spastic tetraparesis with grade 4/5 power for shoulder abduction and hip flexion. Joint position sense in the toes, vibration sense in the feet and pin prick sensation in the fingers were all impaired, as were fine movements of the right hand.

Plain radiographs of the cervical spine showed moderate spondylosis with a borderline canal diameter at C5/6 (mAPD 10.5 mm). Myelography demonstrated severe anterior and moderate posterior cord indentation at C5/6 (fig. 5A). PMCT (fig. 6A, B) additionally revealed severe cord flattening at C5/6 by a diffuse osteophytic protrusion anteriorly and the laminae posteriorly. A central osteophytic protrusion at C6/7 level was shown to be in contact with the anterior aspect of the spinal cord.

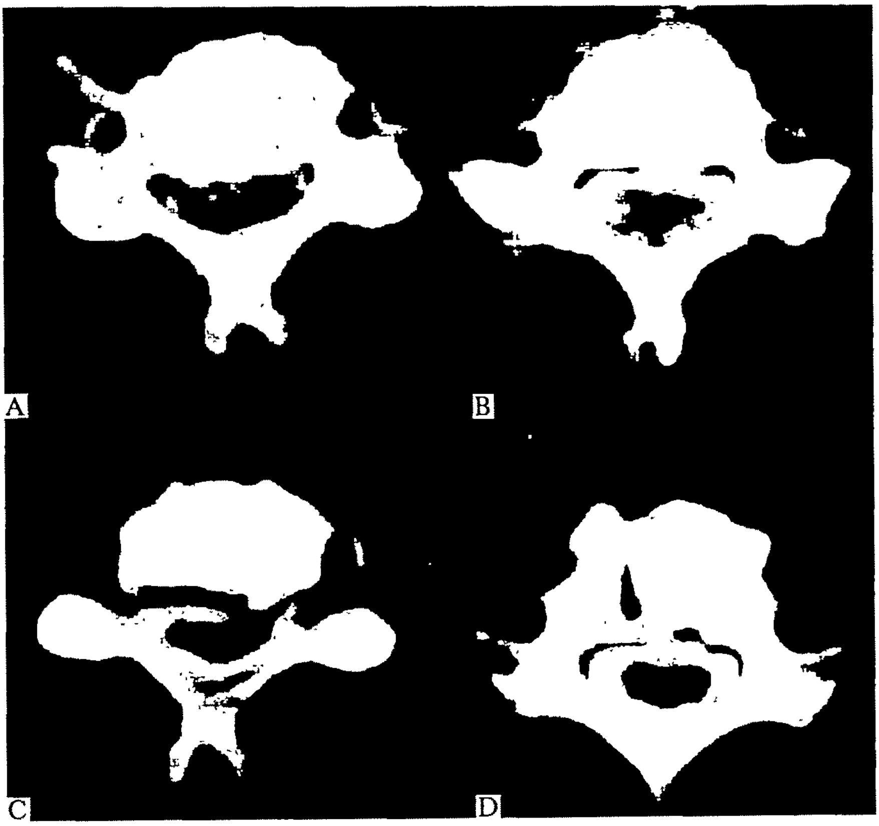

FIG. 6. Postmyelogram computed tomography (PMCT) in Case 10 (cervical spondylotic myelopathy). (A) and (B) show the C5/6 and C6/7 levels preoperatively, with severe anterior and posterior cord flattening, obliteration of the subarachnoid space at the C5/6 level and mild cord deformity from a central osteophyte at C6/7. Following the Cloward procedure, PMCT shows (C), mild anterior cord compression with a residual right lateral osteophyte impinging the subarachnoid space at C5/6 and (D), normal cord configuration at C6/7

Preoperative SEPs were within normal limits following median and ulnar nerve stimulation, but of slightly prolonged latency and very low amplitude for both tibial nerves (fig. 7). This was in keeping with the clinical finding of bilateral posterior column signs confined to the lower limbs.

A Cloward procedure was performed, during which the posterior longitudinal ligament was excised at C5/6 and large osteophytes removed by curettage. Six months postoperatively there was marked improvement in motor function and complete resolution of the sensory disturbance in the right hand. On the left, however, a mild 'surging' sensation extended the length of the arm, trunk and leg. Examination showed normal motor power and no objective sensory deficits, but there were persistently brisk tendon reflexes bilaterally and an extensor plantar response on the left. Myelography (fig. 5B) revealed residual anterior thecal indentation at C5/6, and PMCT (fig. 6C, D) residual anterior cord compression at C5/6, more marked on the right.

Postoperative median and ulnar nerve SEPs showed no significant change compared with the preoperative record, but tibial nerve responses were markedly increased in amplitude and reduced in latency (fig. 7).

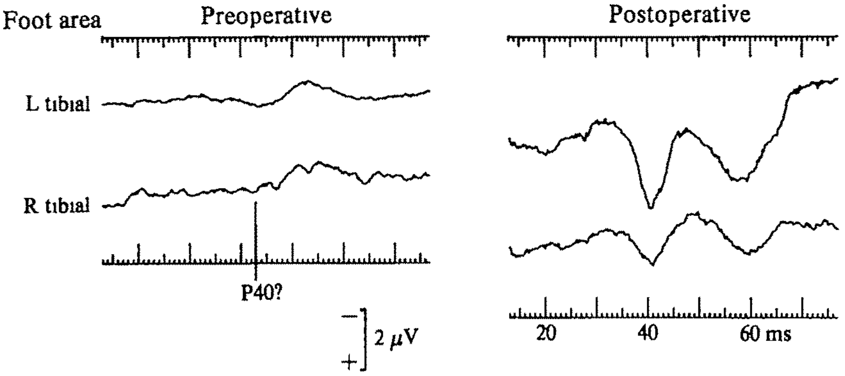

FIG. 7. Preoperative and postoperative tibial nerve SEPs from Case 10 (cervical spondylotic myelopathy). The preoperative record is of abnormally low amplitude (P40 virtually absent on the right) and borderline latency for a woman of average stature, aged 43 years. Postoperatively there was a marked increase in amplitude bilaterally and a slight reduction in latency. This correlated with a substantial clinical improvement.

Case 13 (myelopathy alone), a male business consultant, aged 52 years, had fallen downstairs four years before admission and become tetraplegic with bladder disturbance. He was admitted into a general hospital and treated conservatively. There was gradual recovery, and six months after the accident the residual symptoms consisted only of mild weakness of the left arm and neck pain radiating to both upper extremities. Two years later he noticed progressive weakness and stiffness of both legs, and paraesthesiae in the fingers of both hands. A rigid cervical collar initially conferred partial relief.

On examination, neck movements were limited and painful. There was a mild to moderate spastic tetraparesis, with the right upper limb less affected. Vibration sense was impaired below the knees and there was equivocal impairment of pin prick sensation in all four limbs.

Plain radiographs of the cervical spine revealed moderate spondylosis and a narrow canal (mAPD 10 mm at C3/4). There was also backward subluxation of the C3 vertebra over C4. Myelography showed moderate anterior cord compression at C3/4 and mild posterior indentation. PMCT (fig. 8A) showed moderate anterior cord flattening from C3 downwards, most marked at the C3/4 intervertebral level, and moderate posterior compression on the left. Although precipitated by trauma, the myelopathy was believed to result from the combined effects of spondylosis, subluxation and a constitutionally narrow cervical canal.

Preoperative SEPs were all within normal limits (left median and tibial nerve responses illustrated in fig. 9), in spite of the presence of posterior column signs in the legs.

In view of the more marked cord compression at C3/4, as well as the instability, a Cloward procedure was performed. When reviewed three months later, however, there had been an increase in the stiffness of the lower limbs and the left hand had become wasted. Sensory deficits remained unchanged. Myelography and PMCT (fig. 8B) showed reduced compression anteriorly, but more marked posterior compression. The left median nerve SEP showed significant deterioration of supraclavicular, cervical

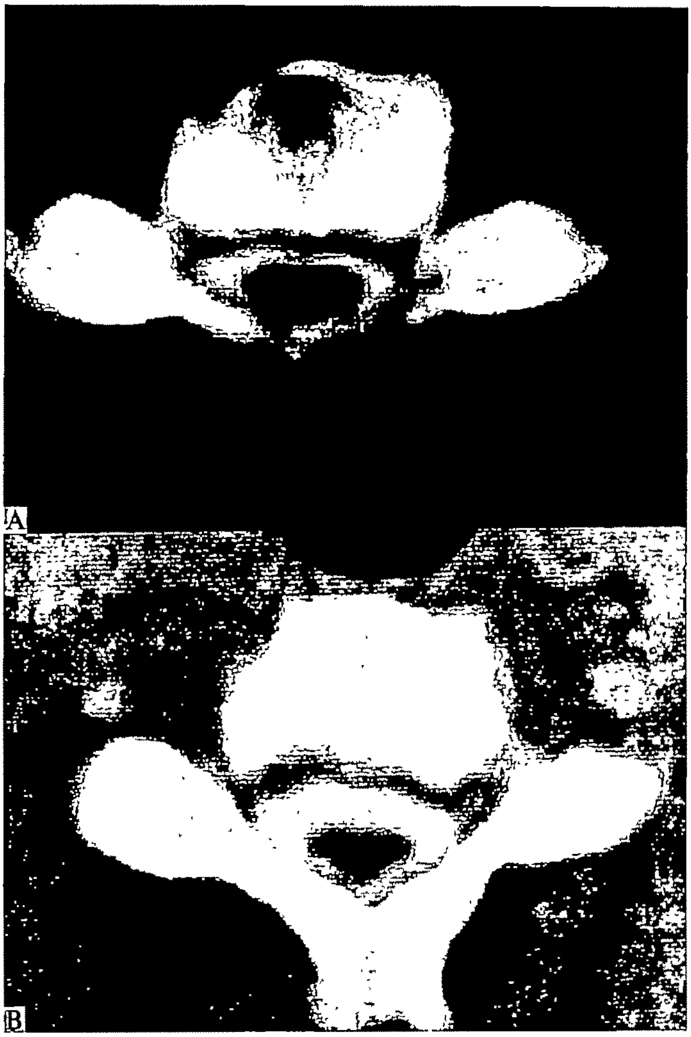

FIG. 8. Postmyelogram computed tomography at C3/4 level in Case 13 (cervical spondylotic myelopathy). The preoperative image (A) shows a narrowed subarachnoid space with anterior cord flattening and moderate posterior cord compression on the left. The postoperative image (B) shows adequate anterior decompression but more marked posterior compression bilaterally. Clinically the patient deteriorated slightly and SEPs were somewhat degraded (*see* fig. 9).

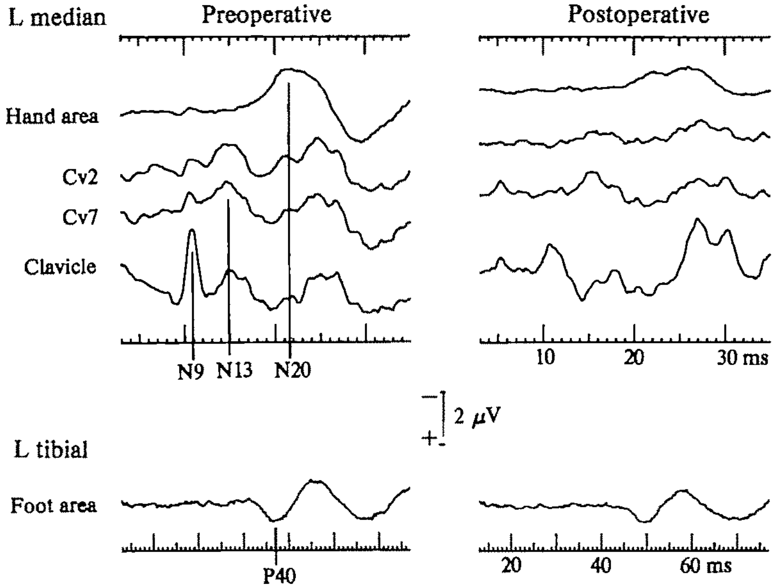

FIG. 9 Preoperative and postoperative median and tibial nerve SEPs from the left side in Case 13 (cervical spondylotic myelopathy), aged 51 years. The median nerve response was within normal limits preoperatively, but clavicular, cervical and cortical components were of reduced amplitude and degraded waveform after operation (distal or ganglionic pattern). The tibial nerve SEP (also initially normal) was slightly reduced in amplitude and increased in latency.

and cortical components (fig. 9), and was now definitely abnormal. Ulnar nerve responses had also deteriorated slightly, and tibial nerve SEPs showed a latency increase of approximately 3 ms at the midline foot area electrode. The patient was offered posterior laminectomy, but opted for conservative treatment.

Radiculopathy

Combined myelopathy and radiculopathy. All 6 patients with radiculopathy in addition to myelopathy (Table 1, fig. 1) had clinical involvement of the C6 root on one or both sides, and 3 had involvement of both C6 and C7 on the same side. In 4 cases, however, median nerve SEPs were within normal limits and in one (Case 6) the wrist on the symptomatic side could not be accessed. This patient had an abnormal median nerve SEP on the contralateral side, in the absence of radicular symptoms. The sixth patient (Case 5, *see* fig. 10) had bilateral median nerve SEP abnormalities which may have been related to bilateral radiculopathy at C5 and C6, but this was considered questionable on account of the fact that ulnar nerve responses were similarly affected, in spite of there being no evidence of root involvement at C8 and/or T1.

Five patients of the combined myelopathy and radiculopathy group had abnormal ulnar nerve SEPs, but in only one of these (Case 3) was there clinical or radiographic evidence of radiculopathy below C7 level (corresponding to a 'distal' ulnar SEP abnormality). In a second patient (Case 4) a 'distal' ulnar SEP pattern on one side may have been related to cervical spondylosis, but a subclinical ulnar nerve lesion was an alternative possibility which could not be excluded. One other patient (Case 2) had evidence of unilateral radiculopathy at C8, but ulnar nerve SEPs were within normal limits. In 4 cases the ulnar SEP abnormality was suggestive of proximal root or spinal cord involvement, but in all of these the latter was considered the more likely explanation as there was no evidence of radiculopathy below C6 on the appropriate side.

Case 5 (combined myelopathy and radiculopathy), a 61-year-old well driller, initially presented with paraesthesiae in all digits, spreading to the forearms and the right leg. Examination revealed impairment of joint position sense in the fingers and unsteadiness of gait. Myelography showed severe anterior and moderate posterior cord compression at C4/5, and a Cloward procedure was performed.

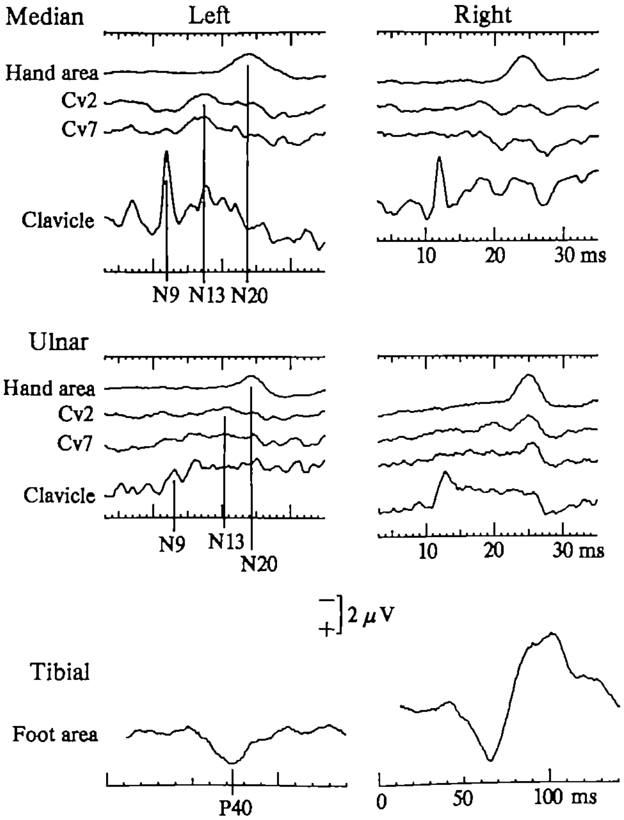

FIG. 10. Median, ulnar and tibial nerve SEPs from the left and right sides in Case 5 (cervical spondylotic myelopathy and radiculopathy), aged 61 years. Cervical potentials were of very low amplitude (within normal limits for the left median nerve only) and the conduction time between clavicular and cervical peaks was prolonged, suggesting a proximal root or spinal cord defect. The abnormal median nerve responses were possibly due to bilateral root lesions at C5/6, but this was considered unlikely in view of the similar defect in the ulnar nerve responses. All abnormalities, including the marked bilateral delay of tibial nerve responses, could be attributed to myelopathy at C5 level.

The symptoms improved, but recurred sixteen months later. A further myelogram showed moderate posterior cord compression at C4/5 and a posterior laminectomy was performed. Symptoms once again improved but deteriorated eight months later, one year before the admission during which SEPs were recorded.

On this occasion neck movements were found to be restricted and painful. There was mild pyramidal weakness in the upper limbs. The biceps and brachioradialis jerks were absent bilaterally. Tendon reflexes were brisk in the lower limbs, with an equivocal left plantar response. Joint position, vibration and pin prick sensation were impaired in the hands, but normal in the feet. Myelography was not performed on this occasion. The overall picture was consistent with a cord lesion at about C5 level, with bilateral radicular involvement at C5 and C6.

SEPs were bilaterally abnormal following median, ulnar and tibial nerve stimulation (fig. 10). Median and ulnar nerve cervical responses were attenuated, with increased N9–N13 conduction times suggestive of proximal root and/or spinal cord lesions. Tibial nerve responses were markedly delayed.

No further investigation or treatment was initiated, since the patient was found to have an abdominal mass and was transferred to another hospital.

Radiculopathy Group

All 6 patients with radiculopathy alone (Table 2, fig. 3) had clinical involvement of the C6 or the C7 root, although none had involvement of both roots on the same side. Radiologically, 2 patients had evidence of C6 and C7 involvement on the same side. Median nerve SEPs, however, were within normal limits in all cases. The single patient (Case 22) with an abnormal ulnar nerve SEP on the right, consistent with a distal or ganglionic lesion at C8 and/or T1, had clinical involvement of only the C5 and C6 roots on the left. The SEP abnormality may have been related to spondylosis, but once again the possibility of a more distal ulnar nerve lesion could not be excluded. In the same patient the tibial nerve SEP was abnormal on the left, but in view of a long history of sciatica this was attributed to a lesion of the lumbosacral roots. One other patient (Case 24, *see below*) had a unilateral abnormality of the tibial nerve SEP, possibly due to subclinical myelopathy. As with the combined myelopathy and radiculopathy group, there was therefore no correlation between SEP abnormalities and the clinical location of radicular lesions.

Plain radiographs showed mild to severe spondylosis in all 6 patients of the radiculopathy group. Foraminal encroachment (not tabulated separately) was demonstrated at more than one level in 4. Root compression was confirmed by myelography and/or PMCT in 5 cases, the sixth being described in detail below. Three patients had mild to moderate anterior and/or posterior cord indentation which was unrelated to their symptoms; all the latter had SEPs which were within normal limits.

Two patients underwent surgery, following which one improved markedly and the other remained unchanged. The postoperative record of the latter showed a slight improvement in the right ulnar nerve response (unrelated to the locus of radiculopathy), although neither pre- nor postoperative SEPs were outside normal limits. Four patients were treated conservatively; at follow-up 3 showed marked improvement and 1 remained unchanged.

Case 24 (radiculopathy alone) was a woman, aged 33. There was a two-month history of severe neck pain radiating to the left upper limb, together with paraesthesiae in the radial three fingers and a numb patch on the lateral aspect of the left arm. Examination showed restriction of neck movements because of pain, reduced left biceps and brachioradialis jerks and decreased pin prick sensation in the lateral aspect of the left arm. In the plain radiographs, mild spondylotic changes without osteophytic foraminal encroachment were seen at C5/C6, and the mAPD was normal (14 mm). Myelography showed mild anterior and posterior thecal indentation not reaching the cord, and the root sheaths were not occluded. PMCT did not add further information. The clinical picture was therefore typical for cervical spondylotic radiculopathy, although radiological confirmation was lacking.

Median and ulnar nerve SEPs were within normal limits, but the latency of N20 was close to the upper limit of normal on the right as compared with the left. The tibial nerve response was significantly delayed on the right. There was no confirmation, therefore, of radiculopathy at C5 and C6 on the left, but some suggestion of subclinical myelopathy on the right. Radicular symptoms improved markedly following use of a cervical collar, and no overt signs of myelopathy developed. In spite of the lack of confirmation, therefore, this illustrates a possible application for SEPs in screening for myelopathy, particularly when radiological investigation is noncontributory.

Neck Pain

Out of 7 patients with a history of neck pain but no clinical signs of radiculopathy or myelopathy, 2 had abnormal SEPs (Table 2, fig. 4). In Case 34 cervical and cortical potentials were of reduced amplitude following stimulation of the right median nerve, and both tibial nerve responses were absent. In Case 28 there was a more equivocal abnormality of both ulnar nerve responses, suggestive of a distal or ganglionic lesion on the left and a proximal root or spinal cord lesion on the right. SEP findings were not related to the presence or absence of sensory symptoms in the arms, nor to the severity and duration of neck pain. Mild to moderate cervical spondylosis was seen in the plain radiographs in all 7 patients, with subluxation at C3/4 in 1 with normal SEPs. Foraminal encroachment was mild to moderate in all 5 patients without SEP abnormalities (at more than one level in 2), but absent in the 2 with abnormal SEPs. All patients were treated conservatively and at follow-up three to fifteen months later, 5 had improved markedly (including Case 28), while none had developed symptoms or signs of radiculopathy or myelopathy.

DISCUSSION

Although there have been many investigations of cervical spondylotic radiculopathy and myelopathy using variations of the SEP technique, it appears that in only five (Fukushima and Mayanagi, 1975; Ganes, 1980; Noël and Desmedt, 1980; Schramm, 1980; Huang, 1983) was the stimulus delivered to sites other than and in addition to the median nerve at the wrist, and in only one of these (Ganes, 1980) were recording electrodes located on the neck as well as the scalp. No previous study attempted more than a superficial correlation of SEP findings with clinical and radiological data. We regard multiple stimulation and recording sites as essential to any serious assessment of the utility of SEPs in this condition, and diagnostic capabilities can only be evaluated in the context of clinical and radiological findings.

Fukushima and Mayanagi (1975) recorded cortical SEPs following median, peroneal and digital nerve stimulation. Only 5 out of 28 recordings obtained from 8 myelopathy cases were judged to be abnormal, correlating with the existence of posterior column signs. Matsukado *et al.* (1976) inserted an electrode into the cervical epidural space, to record the 'spinal electrogram' (median or ulnar nerve stimulation) before and during surgery. From 9 cases with myelopathy and 2 with disc protrusion, abnormal recordings were obtained in 9. The initial component, thought to represent activity in dorsal root fibres, was less affected than subsequent potentials believed to derive from the dorsal horn. A relatively mild degree of abnormality was found to be a good prognostic sign. El-Negamy and Sedgwick (1979) recorded from sites over the brachial plexus and cervical spine following stimulation of the median nerve. Out of 14 patients with myelopathy and radiculopathy, alone or combined, cervical potentials were absent in 5 (4 with combined myelopathy and radiculopathy), delayed in 5 (all with combined deficits) and normal in 4 (3 with radiculopathy alone). A delay between 2 cervical components (N11 and N13) was always associated with myelopathy. Mastaglia *et al.* (1978) reported attenuated or absent cervical potentials in 3 cases of CSM, and Chiappa *et al.* (1980) a delayed cervical response in 1 case with radiculopathy.

Ganes (1980) recorded from three sites over the clavicle, neck and scalp, and stimulated the ulnar as well as the median nerve. SEPs did not differ significantly from normal in patients with pain and paraesthesiae alone, but were significantly affected in an intergroup comparison of radiculopathy cases with controls. 'Variable' results were obtained from patients with myelopathy. Siivola *et al.* (1981) also recording from three sites, detected SEP abnormalities following median nerve stimulation in 6 out of 12 cases with myelopathy. Noël and Desmedt (1980) studied 7 patients with extrinsic cervical cord lesions of various aetiologies, including spondylosis. Cortical SEPs following digital nerve stimulation were delayed in only 2 cases, but sural nerve responses were delayed in all 7. It was suggested that the great distance between cervical posterior column segments deriving from sural nerve fibres and their cell bodies in the lumbosacral dorsal root ganglia might result in greater susceptibility to conduction impairment.

In a preliminary study, Huang (1983) found that cortical responses to stimulation of digital and musculocutaneous nerves reflected the presence or absence of root lesions at C5 to C8 with some accuracy. This is essentially the same approach as that developed more fully by Schramm (1980), stimulating lumbosacral as well as cervical dermatomes. Cortical SEP abnormalities were demonstrated in 15 out of 18 patients with CSM and 11 out of 22 with radiculopathy. More importantly, the pattern of sites from which abnormal responses were evoked was to some degree characteristic of the diagnosis of radiculopathy or myelopathy. Radicular lesions gave rise to mild SEP abnormalities in a single or polysegmental pattern on the appropriate side of the body, whereas myelopathy often resulted in an electrophysiological 'level', below which the stimulus produced consistently abnormal responses. This technique may prove to be more sensitive to radiculopathy than stimulation of large nerve trunks.

Like many previous reports, the present paper describes a high incidence of SEP abnormalities in cervical spondylotic myelopathy but a much lower incidence in cases of radiculopathy. Considering first the latter pathology, the median nerve response was expected to reveal the highest incidence of abnormalities since the sensory fibres gain access to the spinal cord *via* the C6 and C7 roots, which are much more often affected than C8 or T1. In practice, however, the median nerve SEP was found to be the *least* often abnormal in the combined myelopathy and radiculopathy group, abnormalities being apparently unrelated to the clinical locus of radicular lesions, and within normal limits in all cases of the radiculopathy group. It might be argued that in the majority of cases the lesion involved either the C6 or the C7 root but not both, and that input from a single intact root might be sufficient for the response to remain within normal limits. In 3 cases of combined myelopathy and radiculopathy, however, median nerve SEPs were normal in spite of radiculopathy at both C6 and C7 on the same side. An alternative and more likely explanation, therefore, may be that the large diameter fibres responsible for the SEP are relatively spared in spondylotic radicular pathology.

Having established that the SEP abnormalities encountered were mainly, if not exclusively, due to myelopathy, an application can be suggested for the technique in screening radiculopathy and neck pain cases for subclinical spinal cord involvement (particularly since myelopathy is often not reflected in plain radiographs). In established cases of myelopathy, with or without accompanying radiculopathy, cord involvement was most often indicated by abnormal tibial nerve SEPs, even when the clinical level of the lesion was above the root entry level for sensory fibres from the median and ulnar nerves. This is similar to the observation made by Noël and Desmedt (1980) for extrinsic cervical cord lesions of various aetiologies. As argued in the earlier paper, therefore, it may be that posterior column axons are more susceptible to conduction impairment from compression or ischaemia when the involved segments are relatively remote from their cell bodies in the dorsal root ganglia. Consequently it is important to record lower as well as upper limb SEPs when investigating spinal cord lesions at any level.

Abnormality of the tibial nerve SEP was strongly correlated with posterior column signs on the same side of the body, but not with anterolateral column sensory signs. Following the report of Halliday and Wakefield (1963), the association between SEP abnormality and posterior column deficits has become widely accepted. However, in the present study abnormal tibial, ulnar or median nerve SEPs were recorded in 8 out of 21 patients without clinical posterior column signs, while the converse (posterior column signs without SEP abnormality) was found in only 2. SEPs are unlikely to replace clinical sensory examination as a routine screening procedure, but appear to be more sensitive to posterior column involvement as well as being a more objective test.

At least three patterns of abnormality could be distinguished in median and ulnar nerve SEPs, according to whether cervical (N13) or cervical and clavicular (N9) components were affected in addition to the cortical response (N20). Abnormality of

N9 was seen in 6 records following stimulation of the ulnar nerve, and in 1 median nerve recording postoperatively (Case 13). In none of these was it possible absolutely to exclude a subclinical lesion of peripheral nerve fibres, and in one (Case 11) muscle responses were found to be diminished when the ulnar nerve was stimulated above the level of the elbow. However, the development in one case of a 'distal' SEP defect after operation suggests that the dorsal root ganglia may themselves be vulnerable under certain conditions. It was observed by Abdullah (1958) that the ganglia from C6 to C8 may lie partially or completely within the intervertebral foramina, which could render them vulnerable in cervical spondylosis.

The 'proximal' SEP pattern, in which N13 is abnormal relative to N9, was first described in cervical spondylosis by El-Negamy and Sedgwick (1979). Although N13 certainly originates within the CNS, there are likely to be a number of contributary generators between the dorsal horn at C6/C7 level and the lower brainstem (*see* Desmedt and Cheron, 1981, and Jones 1982*a*). In cases of traction injury to the brachial plexus, abnormality of N13 and N20 with N9 relatively unaffected is often seen when roots are avulsed from the spinal cord (Jones, 1979), but a similar pattern in multiple sclerosis (MS) (Jones, 1982*b*) is more likely to be due to a CNS lesion involving the posterior columns. It follows that when the same pattern is observed in cervical spondylosis, it cannot be absolutely ascribed either to radiculopathy or to myelopathy, but in view of the lack of correlation between SEP abnormalities and the clinical locus of root lesions, myelopathy is believed to be the more likely cause in the majority of cases.

The third pattern of upper limb SEP abnormality was one of amplitude reduction or delay between N13 and N20. In patients with cervical spondylosis, this can be assumed to be due to myelopathy, and specifically to involvement of the posterior columns rostral to the appropriate root entry zone. A similar pattern is sometimes seen in MS (Small *et al.*, 1978; Eisen and Odusote, 1980; Jones, 1982*b*). It is desirable to be able to define those SEP features which may serve to discriminate cervical spondylotic myelopathy from MS, and the present data indicate that this may sometimes be possible. When the clinical sensory level is above C6, SEPs to lower limb stimulation are likely to be abnormal in a high proportion of cases with either pathology. Median nerve responses, on the other hand, are usually abnormal in cases of MS with upper limb involvement (Small *et al.*, 1978; Jones, 1982*b*), but may remain within normal limits in cervical spondylosis. In cervical spondylosis, the SEP abnormality is likely to be characterized by loss of amplitude, degradation of waveform and slight delay, whereas in MS marked delays with relative preservation of amplitude and waveform are often seen. Finally, the 'distal' or ganglionic pattern is not encountered in MS (Jones, 1982*b*). The overlap between SEP findings in the two conditions is considerable, but there may still be features suggestive of one pathology rather than the other. SEPs may also be of value in excluding the diagnosis of amyotrophic lateral sclerosis, by demonstrating involvement of the sensory pathway.

In the present study, SEP abnormalities were found to be correlated with myelopathy and posterior column signs, but not with any other clinical features. The lack of correlation with duration of symptoms is consistent with the natural course of cervical spondylotic myelopathy. Lees and Turner (1963), in a study of 44 patients, found that an early phase of deterioration followed by a long period of nonprogressive disability was the rule, and a progressive deteriorating course an exception. Nurick (1972) also observed that, in the majority of his 91 cases, the initial phase of deterioration was followed by a static period lasting a number of years. It was therefore considered that the factors leading to cord impairment might operate for a short time only. The absence of correlation between SEP abnormalities and the degree of functional disability follows largely from the lack of correlation with anterolateral cord signs, since disability is largely defined in terms of motor deficits.

A number of prognostic indicators for cervical spondylotic myelopathy have previously been proposed. Nurick (1972) found that age at presentation was the single factor most associated with subsequent deterioration, older patients being at greater risk. Gregorius *et al.* (1976) followed up 55 patients postoperatively over a mean period of 45 months. The outcome was found to be relatively poor where there was sphincter disturbance or lower limb weakness preoperatively, but was not significantly predicted by other symptoms or by the age of the patient. Guidelines in this respect are of some importance in the selection of cases for surgery, but have yet to be agreed upon. The full prognostic value of the SEP technique for patients treated surgically and conservatively could not be determined from the limited numbers of this study, but might be worth assessing in a larger group. Similarly, if serial SEPs were found to reflect clinical deterioration reliably, they might serve as a screening procedure before repeat myelography were considered.

In the patients of the present study the presence and degree of posterior and anterior cord compression, as seen on myelography and PMCT, were well documented. PMCT is now becoming an established technique for investigation of cervical spondylotic myelopathy and radiculopathy (Coin *et al.*, 1977; Yu *et al.*, 1983). Although the images are usually taken with the neck only in the neutral position, and root involvement is less well shown, PMCT provides useful additional information with regard to the site (anterior, posterior, central, lateral, unilateral, bilateral) and severity of cord compression, as a result of the higher resolving power and the display of a cross-sectional view.

SEP abnormalities, however, were still seen in 6 out of 8 myelopathy cases without radiological evidence of posterior cord compression. One possible explanation for this may be that the compression was missed by both myelography and PMCT, but this is considered unlikely. More plausibly, it has often been suggested that direct compression may not be the only mechanism causing cord damage in cervical spondylosis, and that local impairment of blood supply may be at least as important. Mair and Druckmann (1953) studied the pathology of cervical spondylotic myelopathy in 4 patients. Macroscopically, only anterior compression was seen in 3 cases, and only a relatively minor degree of posterior compression in the last (for whom the major compression site was also anterior). Lesions were found mainly in the anterior horns, the lateral columns and the anterior portion of the posterior columns. Apart from the sparing of the anterior columns, this distribution of lesions suggests the distribution of the anterior spinal artery. Moreover, the histological changes were similar to those seen in ischaemic lesions of the cord.

While compression is undoubtedly an important factor in the pathogenesis of cervical spondylotic myelopathy, it is likely that ischaemia is the final common pathway leading to cord damage. This view is supported by the findings of Gooding *et al.* (1976), who applied experimental compression to the cervical cord in dogs. At the maximum tolerable force (defined as that sufficient to cause minimal weakness in one leg), blood flow was found to be reduced at the compression site. Griffiths (1972) felt that vascular factors were partially responsible for pathological changes caused by thoracolumbar disc protrusion in dogs, but were of secondary importance to compression. Brodkey *et al.* (1972) found that ischaemia played an important part in conduction block caused by compressing the spinal cord in cats. If direct compression is not the sole pathogenic mechanism in cervical spondylotic myelopathy, the present study suggests that SEPs may be a useful adjunct to radiography in diagnosing the condition. It is not clear why cord ischaemia should cause delay, in addition to amplitude reduction, of the cortical SEP, but it is possible that integrative mechanisms at the first synapse in the dorsal column nuclei may cause a degraded spinal action potential to be translated into a delayed postsynaptic volley.

The finding of abnormal SEPs suggestive of myelopathy in 1 case from the radiculopathy and 2 from the neck pain groups is consistent with the observation of Pallis *et al.* (1954) that neurological signs may develop in a 'silent' manner in asymptomatic patients with radiological abnormalities. It remains to be established whether patients with subclinical SEP abnormalities go on to develop overt symptoms of myelopathy, but if so the SEP technique may be of use in screening asymptomatic or mildly affected patients for subclinical myelopathy.

In conclusion, an investigation of the diagnostic utility of the SEP technique in cervical spondylosis, using multiple recording sites with stimulation of the median, ulnar and tibial nerves, has demonstrated a high incidence of detected myelopathy but no correlation with radiculopathy. Routine SEP recordings, particularly using lower limb stimulation, may be a useful adjunct to clinical and radiological examination in the differential diagnosis of cervical cord lesions, and in the detection of subclinical posterior column involvement.

ACKNOWLEDGEMENTS

We wish to thank the physicians and surgeons at the National Hospitals for Nervous Diseases, Queen Square and Maida Vale, for permission to study their patients. We are indebted to Professor G. H. du Boulay who kindly gave us free access to the radiographs, and to Dr A. M. Halliday for helpful advice and criticism.

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(*Received May 1, 1984. Revised September 20, 1984. Accepted September 25, 1984*)

Brain (1985), **108**, 301–313

BRAIN GLUTAMATE DECARBOXYLASE IN PARKINSON'S DISEASE WITH PARTICULAR REFERENCE TO A PREMORTEM SEVERITY INDEX

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SUMMARY

Glutamate decarboxylase (GAD) activity was estimated in various areas of the brain in 21 control and 26 parkinsonian subjects matched for age, postmortem delay and premortem state. Retrospective analysis of clinical data was used to define a premortem severity index (PMSI), scaled from 0 to 6, based upon a semiquantitative estimation of the duration of anoxia (0–3) and hypovolaemia (0–3). A significant correlation was found between GAD activity and PMSI in most regions of the brain. In the prefrontal cortex and caudate nucleus, GAD activity was not correlated with age, postmortem delay, sepsis, being bedridden, or with cachexia. Dosage and duration of drug treatment did not influence striatal or cortical GAD levels. In Parkinson's disease, GAD activity did not differ from controls in many brain areas except in the caudate nucleus, hippocampus and the frontal and occipital cortex. No difference in striatal and cortical GAD activity was observed when 10 control and 9 parkinsonian brains were selected for an optimal premortem state which approximated to sudden death (PMSI $\leqslant 2$). GAD activity in the caudate nucleus and prefrontal cortex was not significantly influenced by the duration of L-DOPA treatment or withdrawal, disease duration, or severity of intellectual deterioration. Although the number of samples in certain brain areas was too small to allow a definitive conclusion, these results make it doubtful that GABAergic neurons are damaged in this disease.

INTRODUCTION

L-glutamate decarboxylase (GAD) (ED-41115), the GABA-synthesizing enzyme, has been used as a marker for GABAergic neurons (Baxter, 1976), since in contrast to GABA itself (Perry *et al.*, 1981), the enzyme is not subject to rapid postmortem changes in activity and can easily be measured. In animals, estimation of GAD activity in relation to localized brain lesions has led to the recognition of GABAergic striatopallidal, striatonigral (Fonnum *et al.*, 1978), pallidothalamic (Penney and Young, 1981) and hypothalamic (Tappaz and Brownstein, 1977) systems, and

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intrinsic striatal neurons (McGeer and McGeer, 1975). In the human brain, the regional distribution of GAD resembles that observed in the rat (Albers and Brady, 1959; Chalmers *et al.*, 1970; Fahn, 1976; McGeer and McGeer, 1976; Tappaz *et al.*, 1976; Mackay *et al.*, 1978; Nieoullon and Dusticier, 1981), suggesting the existence of similar GABAergic systems. In neurological diseases, changes in GAD activity have been detected in postmortem material. In Huntington's disease, the heterogeneous decrease in brain GAD activity (Bird *et al.*, 1973; McGeer *et al.*, 1973; Bird and Iversen, 1974; Urquhart *et al.*, 1975; Spokes, 1980) and GABA concentrations (Perry *et al.*, 1973; Spokes *et al.*, 1980) indicates a diffuse degeneration of GABAergic systems. In Parkinson's disease, reduced GAD activity has been reported in the basal ganglia and substantia nigra (McGeer *et al.*, 1971; Lloyd and Hornykiewicz, 1973; Rinne *et al.*, 1974; Lloyd *et al.*, 1975; Gaspar *et al.*, 1980; Javoy-Agid and Agid, 1980; Javoy-Agid *et al.*, 1981) and could reflect the degeneration of striatopallidonigral GABAergic neurons. This finding should nevertheless be treated with caution since histopathological observations do not favour neuronal loss within the striatum (Greenfield and Bosanquet, 1953). Indeed, GABA levels have also been found to be unchanged (Laaksonen *et al.*, 1975) or even increased (Perry *et al.*, 1983) in the striatum of patients as compared with controls. Moreover in animal studies, destruction of the nigrostriatal dopaminergic pathway, mimicking the dopamine loss in Parkinson's disease, results in an increased striatal GAD activity (Vincent *et al.*, 1978).

GAD sensitivity to premortem conditions (Perry and Perry, 1983), particularly anoxia (Bowen *et al.*, 1976), reduced cerebral blood flow (Bowen *et al.*, 1977) and prolonged periods of illness with coma (Perry *et al.*, 1982), and to postmortem delay (Fahn and Côté, 1976; Puymirat *et al.*, 1979) and storage temperature (Puymirat *et al.*, 1979), has been demonstrated. This is emphasized by the considerable differences in striatal GAD activity observed among control brains from a hospice and a general hospital (Agid *et al.*, 1984). The 70 per cent reduction in GAD activity found in patients from the general hospital as compared with those from the long-stay hospital was most probably related to the intensive care more often administered to the former patients. Thus interpretation of changes in brain GAD activity in Parkinson's disease must be circumspect, since terminal anoxia is frequent due to aspiration pneumonia in such patients.

The purpose of the present study was to analyse various premortem factors which might affect GAD activity. An index of clinical premortem severity (premortem severity index or PMSI) was defined, based on a semiquantitative estimation of terminal anoxia and hypovolaemia. Simultaneously, GAD activity was estimated in a number of brain areas from controls and parkinsonian patients matched for age and sex as well as for their premortem state. The data confirmed that GAD is sensitive to premortem conditions and suggest that the enzyme activity and thus GABAergic innervation is not affected in Parkinson's disease.

MATERIAL AND METHODS

Patients (Table 1)

Among a series of 35 control and 35 parkinsonian brains matched for age, sex and postmortem delay, a group of 21 controls and 26 parkinsonian patients with similar premortem conditions (PMSI, as defined later) was selected for the clinical and biochemical correlation study. Control subjects had no known neurological or psychiatric disease. Parkinson's disease was diagnosed from the clinical findings, the response to L-DOPA therapy, the postmortem estimation of caudate nucleus dopamine content (a minimum decrease of 80 per cent when compared with control values was required for inclusion) and the histopathological changes in the contralateral hemisphere.

TABLE 1. CHARACTERISTICS OF THE 21 CONTROLS AND 26 PARKINSONIAN PATIENTS

	Sex	*Age (yrs)*	*Premortem severity index (PMSI)*	*Postmortem delay (h)*	*Storage time (months)*
Controls	M (13) F (18)	75 ± 3	3.0 ± 0.3	14 ± 1	20 ± 2
Parkinson's disease	M (22) F (4)	72 ± 1	2.8 ± 0.3	16 ± 2	30 ± 3*

The premortem severity index (PMSI) was estimated by summing the hypoxia and the hypovolaemia indices determined for each patient. Postmortem delay was estimated as the time lapse between death and storage of the brain at −70° C. Storage time corresponds to the period of brain storage in deep freeze (−70° C) between autopsy and biochemical assay. * Significantly different when compared with control values according to Student's t test ($P \leqslant 0.05$).

Retrospective Evaluation of the Clinical Cases

The analysis of the case history of each patient included an examination of the case records, a detailed review of drug administration in the period leading up to death, of the bedside charts (temperature, pulse, blood pressure and weight) and of the nursing records (state of consciousness, timing and nature of the drug administration and feeding, intravenous infusions, oxygen therapy, upper airways suction, bowel sounds, blood transfusions, etc.). Cachexia was considered to be present in the case of weight loss, or when feeding was difficult or inadequate for more than a week. Patients were regarded as bedridden when intensively nursed or when treated for bedsores for more than a week. Infection was recorded either for focal infections (pulmonary, urinary or any other) or pyrexia (temperature > 38° C) associated with leucocytosis (> 10000/mm^3). Two further criteria were analysed in greater detail, namely hypoxia and hypovolaemia, and quantification was attempted. This was based on their duration, which was easily and objectively assessed, rather than on their severity which proved to be difficult to estimate. The score appeared to be constant from one examiner to another and was expressed as a hypoxia (I_{O_2}) and a hypovolaemia (I_{vol}) index on a 0 to 3 scale as follows: 0 = absence of hypoxia or hypovolaemia; 1 = duration less than 1 h; 2 = duration between 1 and 24 h; 3 = duration exceeding 24 h. A premortem severity index (PMSI) was derived by summing the two indices (yielding a severity scale from 0 to 6).

In most of the cases, the retrospective analysis of the clinical observations was informative as to the pathological sequence and the circumstances which led to admission to hospital. The cause of death was established from the clinical and anatomicopathological data. The clinical reports on the parkinsonian patients were not accurate enough for a reliable retrospective quantification of the main symptoms nor for the assessment of the presence of side effects such as involuntary movements and fluctuations related to treatment. However, intellectual deterioration could be evaluated from retrospective clinical considerations and from the presence of Alzheimer's type histopathological changes (Dubois *et al.*, 1983). Dementia was classified as severe with prolonged evolution (2), mild and/or recent (1) or nonexistent (0). Postmortem processing of the material was detailed in a card index.

Collection and Dissection of the Anatomical Samples

Within 2 h of autopsy, the brain (cerebellum excluded) was cut in two sagittally along the median line and the hemispheres stored at −70° C until dissection. One hemisphere from the parkinsonian brains was fixed in 10 per cent formaldehyde for anatomicopathological examination. Postmortem delay was estimated as the time between death and storage of the brain at −70° C. When the time of receipt or of storage in deep cold was unclear, a 3 h period (corresponding to the average usual delay) was added to the delay between death and autopsy. Storage time represented the period in deep freeze between autopsy and biochemical assay. Storage time was significantly longer for the parkinsonian than for the control brains (Table 1). Coronal brain slices 10 mm in thickness (1 mm for the brainstem) were cut as described previously (Gaspar *et al.*, 1980; Javoy-Agid *et al.*, 1981). Each structure, taken in its entirety from serial sections, was reduced to powder on dry ice and stored at −70° C until biochemical assay.

Estimation of GAD Activity

10 mg of each structure was homogenized in 10 vols of a 0.2 per cent TRIS-HCL-triton buffer, pH 7.4. After centrifugation, GAD activity was estimated on a 10 μl aliquot of the homogenate by a radioenzymatic method (trapping $^{14}CO_2$ formed from L-[1-^{14}C] glutamic acid) (Puymirat *et al.*, 1979). Protein was determined by the method of Lowry *et al.* (1951). Experimental values were evaluated statistically with Student's t test, the Mann-Whitney U test and the correlation coefficient r (least squares method). Differences were accepted as statistically significant for all P values $\leqslant 0.05$.

RESULTS

Influence of Premortem Factors on GAD Activity in Control and Parkinsonian Brains

The study focused on samples from the caudate nucleus and frontal cerebral cortex (Brodmann area 9) since large numbers could be matched for age, postmortem delay and PMSI. In control as well as in parkinsonian brains, GAD activity was not related to the pathological diagnosis established from the history or by the immediate cause of death. No relationship was evident between enzyme activity and drug treatment in the weeks or days preceding death, nor was GAD activity significantly correlated with age, postmortem delay or storage time (Table 2). In addition, enzyme activity did not differ when samples were compared between patients with or without sepsis or cachexia, or if bedridden (Table 3). A significant correlation was, however, observed between decreased striatal GAD activity and the hypoxia and hypovolaemia indices (Table 2). In the frontal cortex, the decrease in GAD activity was only correlated with hypoxia in the control brains. In both regions the PMSI was inversely correlated with GAD activity. The PMSI

TABLE 2. CORRELATION BETWEEN STRIATAL AND FRONTAL GAD ACTIVITY AND PREMORTEM PARAMETERS

								Duration		
		Age	*Post-mortem delay*	*Storage time*	I_{O_2}	I_{vol}	*PMSI*	*Disease*	*L-DOPA therapy*	*L-DOPA withdrawal*
Controls	CN	0.20	0.20	0.14	0.57*	0.61*	0.94*			
	FC	0.32	0.22	0.24	0.51*	0.01	0.45*			
Parkinson's disease	CN	0.075	0.01	0.10	0.53*	0.41*	0.67*	0.10	0.10	0.01
	FC	0.10	0.10	0.01	0.30	0.37	0.57*	0.01	0.17	0.01

GAD activity was correlated with various premortem characteristics of 21 control and 26 parkinsonian brains Correlation coefficients established by linear regression were statistically significant (*) for all P values $\leqslant 0.05$. I_{O_2} and I_{vol} = hypoxia and hypovolaemia indices. CN = caudate nucleus, FC = frontal cortex.

(which combines both the hypoxia and the hypovolaemia indices) thus appears to be a more accurate parameter for the evaluation of premortem tissue damage than for the two indices taken separately. In some of the other brain regions, the failure to detect a correlation between change in GAD activity and the PMSI (Table 4) could be related to the small number of samples available, particularly in the control group.

In Parkinson's disease, disease duration, the length of L-DOPA treatment and of L-DOPA treatment withdrawal (Table 2), as well as the occurrence and severity of intellectual deterioration (Table 3) did not influence striatal and cortical GAD activity significantly. Yet a significant correlation was observed between the length of cessation of L-DOPA treatment before death and GAD activity in the entorhinal cortex ($r = 0.53$; $P \leqslant 0.05$) and in the substantia nigra, pars reticulata ($r = 0.63$; $P \leqslant 0.05$.

GAD Activity in Brains from Parkinsonian Patients

GAD activity was estimated in 21 control and 26 parkinsonian brains matched not only for the usual parameters (age, postmortem delay), but also for the premortem state (Table 1). The PMSI was not significantly different in the two groups (3.0 ± 0.3 and 2.8 ± 0.3 in controls and parkinsonians, respectively). The enzyme activity was lower than control values in all regions except the entorhinal

TABLE 3 INFLUENCE OF PREMORTEM PARAMETERS ON STRIATAL AND CORTICAL GAD ACTIVITY

		Sepsis		*Cachexia*		*Bedridden*		*Dementia*		
		−	+	−	+	−	+	0	1	2
		(7)	(14)	(11)	(10)	(8)	(13)			
Controls	CN	45 ± 5	43 ± 6	40 ± 6	47 ± 6	45 ± 7	42 ± 6			
	FC	33 ± 5	36 ± 4	37 ± 5	33 ± 4	42 ± 5	30 ± 4			
		(5)	(21)	(6)	(20)	(3)	(23)	(11)	(11)	(4)
Parkinson's disease	CN	34 ± 15	30 ± 5	21 ± 4	35 ± 7	16 ± 3	33 ± 6	25 ± 7	39 ± 9	26 ± 12
	FC	23 ± 3	18 ± 3	22 ± 3	18 ± 3	20 ± 4	19 ± 3	17 ± 3	21 ± 4	15 ± 6

Enzyme activity (nmol/h/mg protein) was estimated in the two brain regions on groups of patients defined according to the presence (+) or the absence (−) of the symptom. No. of brains in brackets. CN = caudate nucleus, FC = frontal cortex.

TABLE 4. CORRELATION COEFFICIENTS BETWEEN GAD ACTIVITY AND PMSI IN VARIOUS STRUCTURES OF CONTROL AND PARKINSONIAN BRAINS

Brain area	*Controls*		*Parkinson's disease*	
Caudate nucleus	0.94***	(21)	0.67***	(26)
Frontal cortex	0.45*	(21)	0.54***	(26)
Occipital cortex	0.59	(11)	0.36	(19)
Cingulate cortex	0.24	(11)	0.59***	(20)
Hippocampus	0.66*	(11)	0.69***	(15)
Entorhinal cortex	0.59*	(11)	0.58**	(16)
Putamen	0.56	(10)	0.59*	(13)
Medial pallidum	0.40	(9)	0.53	(10)
Lateral pallidum	0.47	(9)	0.59	(10)
Substantia nigra, pars reticulata	0.41	(6)	0.64*	(11)
Substantia nigra, pars compacta	0.52	(6)	0.66*	(10)
Subthalamic nucleus	0.39	(5)	0.71**	(10)

Correlations were determined by linear regression and considered as statistically significant for all P values ($\leqslant 0.05$). * $P \leqslant 0.05$; ** $P \leqslant 0.02$; *** $P \leqslant 0.01$. No. of brains in brackets.

cortex. However, the reduction only reached significance in the caudate nucleus, frontal and occipital cortex and hippocampus (*see* fig.)

From this population, 10 control and 9 parkinsonian brains were selected for their optimal premortem condition which approximated to sudden death (PSMI $\leqslant 2$; control 1.8 ± 0.1, parkinsonian 0.9 ± 0.4). The PMSI was not statistically different between the two groups. No difference was observed in striatal and frontal GAD activity between the two groups (Table 5).

TABLE 5 STRIATAL AND CORTICAL GAD ACTIVITY IN CONTROL SUBJECTS AND PARKINSONIAN PATIENTS

	A. Total group		*B. Optimal group*	
	Controls	*Parkinson's disease*	*Controls*	*Parkinson's disease*
Caudate nucleus	44 ± 4	31 ± 5*	62 ± 2	56 ± 10
Frontal cortex	34 ± 3	18 ± 2**	39 ± 3	29 ± 4

GAD activity was measured (A) in 21 control and 26 parkinsonian brains matched for PMSI, premortem and postmortem characteristics (*see* Table 1). * $P \leqslant 0.03$; ** $P \leqslant 0.001$, statistically significant when compared with control values. (B) Among these brains, 10 controls and 9 parkinsonians were selected for their optimal premortem condition, approximating to sudden death (PMSI $\leqslant 2$).

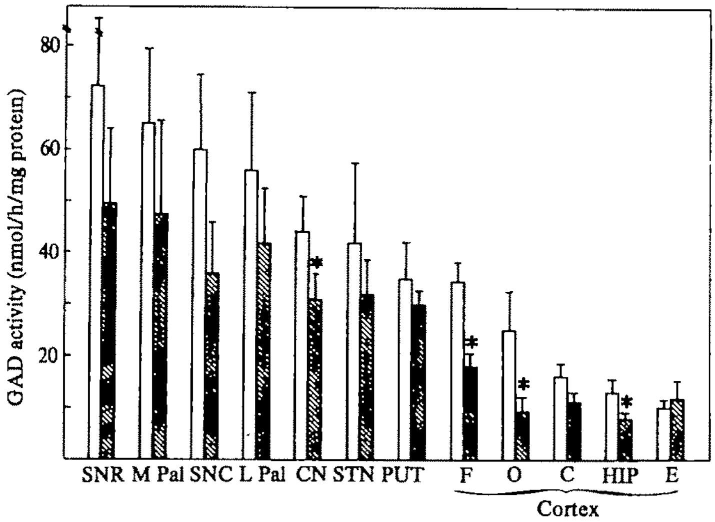

FIG. GAD activity in brains of control subjects and patients with Parkinson's disease. GAD activity was estimated in various areas of control (open columns) and parkinsonian (hatched columns) brains. Caudate nucleus (CN), frontal cortex (F) (21 controls; 26 patients); occipital (O), cingulate (C), entorhinal cortex (E) and hippocampus (HIP) (11 controls; 15–19 patients); putamen (PUT), medial (M Pal.) and lateral (L Pal.) pallidum (9 controls; 10 patients); substantia nigra, pars compacta (SNC) and reticulata (SNR), subthalamic nucleus (STM) (6 controls; 10–11 patients). Statistically significant when compared with control values (* $P \leqslant 0.05$).

DISCUSSION

GAD Activity in Postmortem Human Brain: a Marker for GABAergic Neurons or an Index of Premortem Conditions?

GAD is known to be a fragile enzyme. Although remarkably stable in tissues stored at −70° C, enzyme activity decreases by 60 per cent within three months at −35° C, and completely disappears within one week at 4° C (Puymirat *et al.*, 1979). Experiments in animal as well as human material have demonstrated an influence of the postmortem delay on GAD stability. Enzyme activity remains fairly stable in the first few hours postmortem, but slowly declines over a period of 48 to 72 h (Fahn and Côté, 1976; McGeer and McGeer, 1976; Puymirat *et al.*, 1979; Spokes, 1979). GAD activity also declines as a function of age, more rapidly in the first part of life (Bird and Iversen, 1974; McGeer and McGeer, 1976; Perry *et al.*, 1983). However, age, postmortem delay of less than 48 h and storage time at −70° C are not helpful in the interpretation of biochemical data. Higher striatal GAD activity has even been reported in elderly people as compared with younger subjects (Agid *et al.*, 1984); all patients from the latter group, however, had been under intensive care just before death. The importance of the terminal conditions on tissue GAD stability has previously been emphasized (Bowen *et al.*, 1976, 1977; Spokes, 1979; Spokes *et al.*, 1979). Enzyme activity is clearly higher following sudden death than in chronically bedridden patients (Perry *et al.*, 1982). The present data indicate that in contrast to other premortem conditions (*see* Table 3), anoxia and hypovolaemia are critical factors involved in enzyme degradation (Tables 2, 4).

Finally, in animal experiments a lesion-induced decrease in GAD activity is usually considered to reflect a neuronal degeneration. In human material from autopsy, because of the enzyme sensitivity to pre- or postmortem factors, the conditions immediately before death must be carefully clarified before a decrease in GAD activity can be interpreted as reflecting GABAergic denervation.

Premortem Severity Index (PMSI)

GAD sensitivity to premortem states may represent a useful indicator of tissue damage. In addition, enzyme activity might provide an index as to how well-matched human autopsy samples are for premortem conditions. Anoxia and hypovolaemia were the only parameters examined in this study which significantly influenced brain GAD activity. An index combining these two factors, the PMSI, was devised in order to assess brain tissue damage and to match control and pathological material adequately. The following conclusions emerged. (1) A detailed examination of the case records from control and parkinsonian patients indicated that GAD activity was not related to previous episodes of anoxia or hypovolaemia, but rather to their premortem incidence. (2) The arbitrary 0 to 3 rating scale reflected the duration rather than the severity of the hypovolaemic and anoxic episodes. Severity must surely play a major role and its determination would contribute to a better estimation of brain damage; however, it proved to be difficult to evaluate consistently. Nevertheless, a careful study of temperature and intensive care charts, and especially of the nursing records (meals, oxygenation, drug regimen, blood pressure, etc.) in most cases permitted an assessment of the duration of symptoms. Thus the two indices can only be considered to be an approximate quantification of the symptoms. (3) GAD activity was inversely related to the duration of hypoxia in some but not all the brain areas examined (i.e. not in samples of parkinsonian frontal cortex). Similarly, the negative correlation between enzyme activity and hypovolaemia reached significance only in the caudate nucleus (Table 2). On the other hand, the PMSI, a simultaneous evaluation of both the hypoxia and hypovolaemia indices, was significantly correlated with the decreased enzyme activity in the caudate nucleus and frontal cortex, as well as in many other brain areas (Table 4). (4) According to the present findings, the most accurate biochemical data should be obtained from studies of patients with a low PMSI (< 2). This optimal condition which approximates to sudden death, although ideal, is possibly not feasible since the number of brains available for biochemical purposes would be diminished. Thus in the present population only 9 of the 26 parkinsonian brains and 10 of the 21 controls would have been suitable, excluding much valuable pathological material.

The moderate change in GAD activity observed between the 21 control and 26 parkinsonian brains with matched premortem and postmortem characteristics

(Table 5) was possibly related to the difference in severity of anoxia and hypovolaemia in control (less severe) and parkinsonian (more severe) subjects, although the duration of these symptoms (as expressed by the PMSI) was similar. Finally, the interpretation of biochemical changes in relation to pathology in autopsy material requires a detailed knowledge of each patient's case history in order to match the groups of brains adequately. A number of conditions are imperative, namely a large number of samples (Spokes, 1979; Agid *et al.*, 1984), an exhaustive clinical and anatomicopathological analysis of each case, a systematic consideration of drug treatment since drugs are liable to interfere with neurotransmitter receptor binding sites, and matching patients for age (McGeer and McGeer, 1976; Carlsson *et al.*, 1980), postmortem delay, and premortem events (Tables 1–5). Attention must be paid to the terminal conditions, mainly the incidence of anoxia and hypoxia, but also possibly other factors not yet evident. The estimation of a PMSI as proposed in the present study only represents a preliminary attempt, which should certainly be improved, particularly if the intensity as well as the duration of the symptoms are ascertained.

GABAergic Systems in Brains of Patients with Parkinsons's Disease

GAD activity was measured in several brain areas of 21 controls and 26 parkinsonian patients, matched for age, postmortem and premortem conditions (Table 1). No significant difference was observed in many structures between the two groups of subjects. Enzyme activity was significantly reduced in the caudate nucleus and several cortical areas (*see* fig.). These findings suggest that GAD activity is not affected in most areas of the parkinsonian brain, which contrasts with the decrease previously reported in the basal ganglia, substantia nigra and cortical areas (McGeer *et al.*, 1971; Lloyd and Hornykiewicz, 1973; Rinne *et al.*, 1974; Lloyd *et al.*, 1975; McGeer and McGeer, 1976; Gaspar *et al.*, 1980; Javoy-Agid and Agid, 1980; Javoy-Agid *et al.*, 1981). These previous observations were mostly derived from small populations of patients and the premortem condition both in control and parkinsonian patients was not extensively described. The reduced GAD activity might thus be indicative of the vulnerability of the enzyme to premortem conditions (the terminal state of parkinsonian patients is often dominated by the occurrence of aspiration pneumonia, an obvious cause of anoxia) rather than to the degeneration of GAD-containing neurons. Indeed, when 10 control and 9 parkinsonian patients were selected for their low PMSI in the present study, a situation close to sudden death, striatal and cortical GAD activity appeared to be unaffected in Parkinson's disease (Table 5). The study was not extended to other brain areas because of the small number of samples that could usefully be matched; no definite conclusions can therefore be drawn, particularly for the substantia nigra. These findings are in accordance with the normal CSF GABA levels recently found in patients with Parkinson's disease (Bonnet *et al.*, 1985), although CSF GABA levels are usually considered to be reduced (Manyam *et al.*, 1980; Teychenné *et al.*, 1982; de Jong *et al.*, 1984). In addition, GABA levels are not different from controls

(Rinne *et al.*, 1979; Kopp *et al.*, 1983) or even increased (Perry *et al.*, 1983) in the striatum of parkinsonian patients. If GABA systems are anatomically intact, the modifications in nigral GAD activity (Lloyd and Hornykiewicz, 1973) and GABA content in the putamen (Perry *et al.*, 1983) could be related to a change in the activity of GABAergic neurons. The restoration of nigral GAD activity (Lloyd and Hornykiewicz, 1973) and CSF GABA content (de Jong *et al.*, 1984) to normal in patients under long-term antiparkinsonian therapy has been attributed to a possible compensatory mechanism (Lloyd and Davidson, 1979). In the present study, a detailed examination of the antiparkinsonian therapy (time of administration, daily dosage, delay between last drug intake and death) did not confirm this assumption. To our knowledge, few pharmacological trials to stimulate GABAergic receptors, or to increase brain GABA levels in parkinsonian patients have been attempted (Bergmann *et al.*, 1984). According to the present data, it would seem unlikely that GABAergic replacement therapy would be effective in this neurological disease. Finally, these results strongly suggest that GABAergic systems in the frontal cortex and caudate nucleus are spared in Parkinson's disease. Moreover, they cast some doubt on the integrity of GAD-containing neurons in other brain areas, such as the substantia nigra, although the number of samples studied was too small for a definite conclusion to be drawn.

ACKNOWLEDGEMENTS

The authors wish to thank A. Ploska for technical help and Mrs J. Sage for assistance in preparing the manuscript. Drs Beck, Bouchon, Piette, Forette (Hôpital Charles Foix, Ivry/Seine) are gratefully acknowledged for providing human material. The study was supported by INSERM (PRC Santé Mentale et Cerveau) and CNRS (Jeune Equipe).

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(*Received June 26, 1984. Revised September 18, 1984. Accepted September 25, 1984*)

Brain (1985), **108**, 315–334

CHANGES IN LYMPHOCYTE SUBSETS DURING THE COURSE OF EXPERIMENTAL ALLERGIC NEURITIS

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SUMMARY

The percentages of various leucocyte subsets in the blood, spleen and popliteal lymph nodes of animals with experimental allergic neuritis (EAN) were determined at various times between the initiation of the disease and recovery. The total cell yield from these tissues and the weights of the spleens and lymph nodes were recorded. Clinical and histological signs of disease were assessed at the same time points. Normal and adjuvant control animals were also studied. The most marked change observed was that the percentage of MRC OX 8^+ ('suppressor/cytotoxic') cells in the blood of animals with EAN was significantly below the normal value during the most severe clinical disease, and then returned to normal during recovery. Adjuvant controls did not show this change. No significant differences were observed in the other lymphocyte subsets studied (surface Ig^+, Ia^+, $W3.13^+$ and $W3.25^+$ cells) or in the total white cell count in the blood. There were no changes from normal values in any of the parameters examined in the spleen. The popliteal lymph nodes were enlarged in both adjuvant controls and animals with EAN and both showed a decrease in the percentage of $W3.25^+$ lymphocytes from normal unenlarged nodes.

INTRODUCTION

Experimental allergic neuritis (EAN), a disease initiated by the injection of peripheral nerve material in Freund's complete adjuvant (Waksman and Adams, 1955, 1956) is important as a possible experimental model of the Guillain-Barré syndrome (Arnason, 1984). It is characterized by an infiltration of lymphocytes and macrophages into peripheral nerves and by extensive demyelination (Ballin and Thomas, 1969; Lampert, 1969) resulting in weakness or paralysis, usually of the hindlimbs and tail but often of forelimbs and facial muscles as well. It is believed to be due to an autoimmune attack against components of peripheral nerve myelin including the protein P_2 (Carlo *et al.*, 1975; Kadlubowski *et al.*, 1980). Galactocerebroside may also be implicated (Saida *et al.*, 1981). Affected animals that do

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not die usually make a good recovery and many are then resistant to further attempts to induce disease (Pollard *et al.*, 1975; Brosnan *et al.*, 1984). It is not clear why the injection of peripheral nerve and adjuvant triggers this autoimmune reaction nor why the reaction is self-limiting. Although the overall response is antigen-specific in that other body tissues are not affected, there could also be a more generalized effect on the immune system since perturbations in lymphocyte subsets have been found in other diseases which are possibly autoimmune in origin, including experimental allergic encephalomyelitis (EAE) (Traugott *et al.*, 1978), the Guillain-Barré syndrome (Hughes *et al.*, 1983), multiple sclerosis (Santoli *et al.*, 1978; Reinherz *et al.*, 1980), systemic lupus erythematosus (Morimoto *et al.*, 1980), rheumatoid arthritis (Fox *et al.*, 1982), myasthenia gravis and autoimmune hepatitis (Bach and Bach, 1981). In the human diseases a common finding is a decrease in the percentage of OKT8$^+$ cells ('suppressor/cytotoxic' cells) and an increase in the OKT4$^+$/OKT8$^+$ ('helper/suppressor') cell ratio in the blood during acute disease, usually with a return to normal or near normal values during remission.

In this report the fluctuations in percentages of several lymphoid populations were studied during the course of EAN. These populations were examined in the lymph nodes draining the inoculation site, in the spleen and in the blood, and observations were made frequently from five days after injection of nerve until after recovery.

MATERIAL AND METHODS

Animals

Male Lewis rats were obtained from the inbred colony maintained at the Royal Free Hospital School of Medicine. Animals were used when between 9 and 20 weeks old.

Preparation of Antigen

Antigen was prepared by the method of King *et al.* (1983). Bovine spinal cords and attached roots were obtained from an abattoir and the intradural dorsal roots extracted and stored frozen until use. When required the dorsal roots (BDR) were transferred to a flow cabinet, cut into small pieces with a scalpel, and then cut three times on a freezing microtome at 5 μm. Complete Freund's adjuvant (CFA) was prepared by adding 3 mg/ml *Mycobacterium butyricum* (Difco) to incomplete Freund's adjuvant (Sigma). CFA was added to the cut nerve at 1.5 ml/g nerve and sterile 0.9 per cent saline added at about 15 drops/g. The mixture (BDR/CFA) was emulsified in an electric blender at 4000–6000 r.p.m.

Injections

EAN was induced by the injection of 0.02 to 0.03 ml BDR/CFA into each hindfoot pad. Control rats for the effects of CFA were injected with the same amount of saline/CFA, made by emulsifying equal volumes of 0.9 per cent saline and CFA.

Clinical Assessment

Animals were weighed and assessed daily for clinical signs of disease. A clinical grade between 0 and 10 was allocated according to the criteria of King *et al.* (1983) (Table 1).

TABLE 1 CLINICAL EVALUATION OF ANIMALS WITH EXPERIMENTAL ALLERGIC NEURITIS

Grade	*Clinical assessment*	
0	Normal	
1	Less lively	Mild
2	Impaired control of landing when falling Slightly slow righting of body position	
3	Very slow or absent righting Limp tail	
4	Ataxic gait Abnormal body position	
5	Mild paraparesis	Moderate
6	Moderate paraparesis	
7	Severe paraparesis	
8	Tetraparesis	Severe
9	Moribund	
10	Dead	

Extraction of Tissues for Analysis

At various times after injection animals chosen at random were killed. They were anaesthetized with ether and intramuscular Hypnorm (Janssen) (0.5 ml/kg body weight). The popliteal lymph nodes were exposed and carefully excised, avoiding any excessive bleeding. The sciatic and sural nerves were partially exposed during this procedure and to prevent these tissues drying out, swabs of gauze soaked in saline were placed over the nerves. The spleen was then removed through a midline laparotomy. The diaphragm and ribs were cut and 4 ml of blood obtained by cardiac puncture. The animal was then perfused *via* the descending aorta with dilute Karnovsky's (1965) fixative as described by King *et al.* (1983). The sciatic, sural, dorsal and ventral lower lumbar and sacral spinal roots, dorsal root ganglia and spinal cords were removed.

Histology

Perfused nerve tissue was fixed for a further 3 h in Karnovsky's fixative at 4° C and then processed for light and electron microscopy as described by King *et al.* (1983). Sections were examined blind for histological signs of disease. Each sample of peripheral nerve tissue examined, that is, sural, sciatic, dorsal root, ventral root and dorsal root ganglion, was given a score of 0 to 3 for the severity of each type of pathological change, namely demyelination, remyelination, axonal degeneration, sprouting, infiltration by macrophages and infiltration by other cells (predominantly lymphocytes). A score of 0 indicated no or very minimal signs, 1 indicated that up to about one-third of the fibres in the nerve were affected, 2 indicated that one to two-thirds of the fibres were affected and 3 indicated that more than two-thirds of the fibres were affected. The scores were totalled for all the tissues (maximum score, 15) and the percentage grade determined for each histological feature.

Preparation of Single Cell Suspensions

All cell suspensions were made in Dulbecco's A+B medium (DAB) (Oxoid) containing 2 per cent newborn calf serum (NCS) (Sera-Lab.) and 10 mM sodium azide. Cell counts and viabilities were assessed in a haemocytometer with 0.2 per cent nigrosin.

Blood was drawn from the heart into a syringe containing 1 ml of medium supplemented with 200 units of heparin (Weddel) per ml. An aliquot was removed for smearing and the rest was mixed with four to five times its own volume with NH_4Cl solution (8.3 g/l). The cells were incubated at room temperature for 10 min to lyse erythrocytes, pelleted, reincubated with NH_4Cl solution, counted and then washed three times in medium.

The weights of the lymph nodes and spleens were recorded immediately after extraction. Lymph nodes were teased apart with needles and debris filtered out with two layers of lens tissue. Analyses of cells before and after filtration through lens tissue did not indicate any preferential removal of leucocyte subsets. Aliquots were removed for smearing and counting and the cells then washed three times in medium. Spleens were cut into small pieces with scissors and pushed through a tea strainer. The cells were filtered through two layers of lens tissue, aliquots removed for smearing and counting and the remaining cells pelleted. The pellet was resuspended in NH_4Cl solution, incubated at room temperature for 10 min and then washed three times in medium. The cells were filtered through lens tissue before the last wash to remove any clumps that appeared after red cell lysis.

Smears

Spleen and lymph node aliquots were centrifuged, resuspended in filtered NCS and smeared. Smears were made from whole blood without any prior manipulation. All smears were air-dried and stained with Romanovsky's stain.

Antibodies

Fluorescein conjugated $F(ab')_2$ fragment goat antirat IgG (GAR-FITC) (Cappel, USA) was used at a 1 in 50 dilution in DAB/2 per cent NCS/10 mm sodium azide. Fluorescein conjugated $F(ab')_2$ fragment sheep antimouse IgG (SAM-FITC) (Cappel, USA) was used at a 1 in 75 dilution and routinely blocked with 15 per cent Lewis rat serum to prevent cross reactivity with rat IgG. Mouse monoclonal antibodies MRC OX 8, MRC OX 3 and W3.13 were used at 20 μg/ml and W3.25 at 40 μg/ml (all Sera-Lab.); for specificities *see* Table 2.

Fluorescence-labelling of Cell Subpopulations

Aliquots of up to 5×10^6 cells of the washed lymph node, spleen and blood preparations were made, centrifuged, and the supernatant removed.

Single stage labelling. The percentages of surface Ig^+ cells (B cells) in the preparations were determined by single stage labelling. The cells were resuspended in 50 μl of GAR-FITC and incubated on ice for 1 h with resuspension every 15 min. They were washed three times and resuspended in 1 ml of 1 per cent formalin in DAB/2 per cent NCS/10 mM sodium azide.

Two stage labelling. The percentages of $W3.13^+$ cells (T cells), MRC OX 8^+ cells ('suppressor/cytotoxic' T cells), $W3.25^+$ cells ('helper' T cells) and MRC OX 3^+ cells (Ia^+ cells) were determined by two stage labelling. The cells were resuspended in 50 μl of the appropriate antibody solution and incubated for 1 h as for single stage labelling. They were washed three times and then resuspended in 50 μl of SAM-FITC and incubated for a further hour. After this they were washed another three times and finally resuspended in 1 per cent formalin in medium.

Controls. Aliquots were also labelled with SAM-FITC alone to control for nonspecific labelling. Background fluorescence was subtracted from specific fluorescence. Lymphocytes gave 1 to 6 per cent nonspecifically labelled cells.

Analysis of Labelled Cells

The fixed cells were kept in the dark at 4° C until analysis on an Ortho Cytofluorograph 50H. The percentages of cells labelled by the antibodies were recorded for the whole population, the population having light scattering properties of lymphocytes, and also the population having greater 90 deg and/or forward scatter than lymphocytes. Laser power was 250 mW.

TABLE 2 LABELLING CHARACTERISTICS OF MOUSE ANTIRAT MONOCLONAL ANTIBODIES

Monoclonal antibody	*Specificity*	*References*
W3.13	All T cells	Williams *et al.* (1977)
	All thymocytes	Williams *et al.* (1977)
	Polymorphs	Williams *et al.* (1977)
	Brain	Williams *et al.* (1977)
	Some natural killer cells and antibody-dependent cellular cytotoxic cells	Cantrell *et al.* (1983)
	B cell precursors	Dyer and Hunt (1981)
W3.25	Helper T cells	White *et al.* (1978) Brideau *et al.* (1980)
	90–95% thymocytes	Brideau *et al.* (1980)
	Macrophages	Barclay (1981)
MRC OX 8	Suppressor T cells	Brideau *et al.* (1980)
	Cytotoxic effector T cells	Dallman *et al.* (1982)
	Cytotoxic T cell precursors	Dallman *et al.* (1982)
	Some natural killer and antibody-dependent cellular cytotoxic cells	Cantrell *et al.* (1983)
	90% thymocytes	Brideau *et al.* (1980)
MRC OX 3	Ia antigens (polymorphic; labels Lewis)	McMaster and Williams (1979)

Significance

Assuming a normal distribution, the 95 per cent confidence limits for the percentages of cells in each subset was calculated for the normal uninjected controls. Results from experimental animals were considered significant if they fell outside this range.

RESULTS

The purpose of this investigation was to study lymphocyte subpopulations during the course of EAN and to correlate any changes with the clinical and histological signs seen in the experimental animals. Two separate experiments were conducted. The results of these have been combined as identical observations were made in both experiments.

A total of 43 rats (22 in one experiment and 21 in the other) were injected with BDR/CFA to induce EAN (day 0). Clinical assessment was made daily from the day of injection until all rats had been killed. At various times (Table 3) after injection 4 rats were killed (3 rats on day 36) and were examined for the following: (1) histological signs of disease; (2) changes in weights or cell numbers in the spleen, lymph nodes and blood; (3) changes in the cell populations in these organs as assessed morphologically in smears; and (4) changes in the cell populations of these organs as assessed by labelling with antibodies directed at various lymphocyte subsets.

A further 8 rats were injected with saline/CFA on day 0 and assessed in pairs as above to control for adjuvant effects. During the same time period a total of 8 age-matched untreated rats were killed in pairs and similarly analysed.

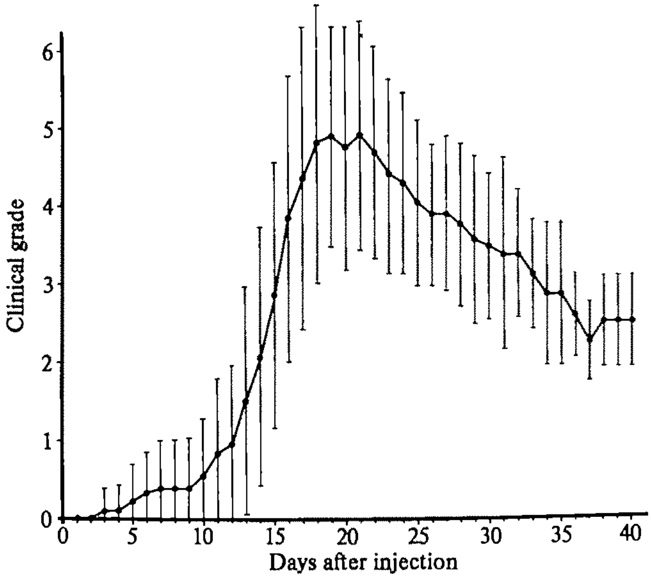

FIG. 1. Clinical grades of rats with EAN. Rats were injected with BDR/CFA on day 0 and assessed daily as in Table 1. The numbers assessed on each day varied with time since rats were killed at various times throughout; n = 43 at day 0. n = 4 at day 40. Results in this and all other figures are shown as mean ± SD.

Clinical Assessment

Clinical grades were assessed daily and the means and standard deviations are shown in fig. 1. The clinical grades of the rats killed at each time point are shown in Table 3. The maximum grade reached by animals which had not been killed before the start of their recovery (21 rats) varied between 3 and 8 (mean ± SD: 5.9 ± 1.3), and the time taken to reach the maximum grade was between 14 and 25 days (18.9 ± 2.7 days). Normal controls showed no signs of disease. Saline/CFA controls showed signs of adjuvant arthritis including weight loss, swelling of the injected foot pads and ankles, occasional ulceration and some hindlimb awkwardness when walking or when landing if dropped from a low height. These controls could be distinguished from animals with early EAN since they showed only signs of pain and stiffness due to swelling with no actual weakness of the hindlimbs and did not show the other signs of EAN such as tail limpness, facial and forelimb weakness, respiratory distress and incontinence. There was no progression to marked loss of limb control or paralysis in the adjuvant control group.

TABLE 3. CLINICAL GRADES OF INDIVIDUAL RATS KILLED AT VARIOUS TIMES

Day of sacrifice[a]	*Clinical grade*[b]
5	0, 0, 0, 0
8	0, 0, 0, 1
12	0, 0, 2, 2
15	1, 2, 2, 3
19	4, 5, 5, 6
22	5, 5, 6, 6
26	3, 3, 4, 5
29	2, 2, 4, 5
33	3, 3, 3, 3
36	2, 3, 3
40	2, 2, 3, 3

[a] Rats were injected with BDR/CFA on day 0. [b] Clinical grade on day of killing. Grades determined as in Table 1.

Histological Assessment

Percentage scores were determined for histological signs of disease for each animal and the results are presented in Table 4. Individual histological evidence of EAN correlated well with the clinical grades allocated.

Uninjected controls had no evidence of current or previous demyelination or axonal degeneration. No macrophages were observed in the nerves but the occasional lymphocyte was seen in the dorsal root ganglia. Animals given saline/CFA were histologically indistinguishable from the normal controls. Clinical and histological signs of EAN occurred concurrently after injection of BDR/CFA

TABLE 4. HISTOLOGICAL SCORES[a]

Injection	*Day of sacrifice*[b]	*Demyelination*	*Remyelination*	*Axonal changes*	*Sprouts*	*Infiltrating macrophages*	*Lymphocytes*
—[c]	—	0	0	0	0	0	3 ± 4
Saline/CFA[d]	8	0	0	0	0	0	3 ± 5
	22	0	0	0	0	0	7 ± 0
	29	0	0	0	0	0	3 ± 5
	40	0	0	0	0	0	7 ± 0
BDR/CFA[e]	5	0	2 ± 3	0	2 ± 3	0	3 ± 4
	8	0	2 ± 3	0	0	0	5 ± 6
	12	1 ± 1	2 ± 4	0	0	0	4 ± 5
	15	3 ± 4	2 ± 4	0	0	5 ± 5	22 ± 16
	19	26 ± 11	2 ± 3	11 ± 8	0	33 ± 16	60 ± 12
	22	34 ± 13	26 ± 9	26 ± 12	13 ± 16	47 ± 11	54 ± 7
	26	15 ± 6	12 ± 11	15 ± 18	3 ± 3	27 ± 15	38 ± 18
	29	14 ± 10	31 ± 24	18 ± 12	11 ± 11	39 ± 20	42 ± 11
	33	20 ± 7	26 ± 10	18 ± 4	20 ± 19	29 ± 6	42 ± 16
	36	16 ± 7	34 ± 10	10 ± 3	7 ± 13	28 ± 5	29 ± 17
	40	11 ± 6	33 ± 10	9 ± 13	23 ± 14	24 ± 12	32 ± 10

[a] Expressed as a percentage of maximum possible score (mean ± SD). [b] Rats were injected on day 0. [c] n = 8. [d] n = 2.
[e] n = 3 for day 36, n = 4 for all other days.

(compare fig. 1 and Table 4), there being no apparent abnormalities of the nerves on days 5 and 8, minimal signs on day 12 and definite disease by day 15. Lymphocyte infiltration was very apparent by day 15 and by day 19 marked macrophage infiltration and demyelination were also observed. Demyelination and macrophage and lymphocyte infiltration scores were highest on days 19 and 22, the same time as clinical disease was most severe. During clinical recovery these features remained prominent although decreasing in magnitude. Remyelination first became apparent at the commencement of clinical recovery at day 22. Axonal degeneration was first observed on day 19 when disease was already severe and sprouting occurred slightly later. Some spinal cords had mild meningitis and there were dorsal column changes in animals with severe EAN, but there was no sign of concurrent EAE activity.

Organ Weights and Cell Numbers

The blood white cell count from normal control rats was $9.8 \times 10^6 \pm 2.6 \times 10^6$ per ml blood (mean ± SD). The counts from animals given EAN and from adjuvant controls were not significantly different from those of the normal rats at any time.

The spleens from normal control rats had weights of 0.70 ± 0.06 g and cell counts of $5.1 \times 10^8 \pm 1.6 \times 10^8$ per spleen. No significant differences were observed at any time between these results and those from the group of rats given EAN or the group given adjuvant alone.

The weights recorded from the popliteal lymph nodes are shown in fig. 2. The lymph nodes increased in weight about twelve-fold after injection of either saline/CFA or BDR/CFA. The enlargement was marked at day 5 and reached a maximum at 8 days after injection. No reduction in size had occurred by day 40. Recovery from both of the popliteal lymph nodes from normal control rats was $2.9 \times 10^6 \pm 0.7 \times 10^6$ cells. After injection of saline/CFA or BDR/CFA cell numbers were significantly higher on day 5 and rose to $9.2 \times 10^7 \pm 2.0 \times 10^7$ on days 8 to 40. Thus the cell numbers reflected the node weight increase, although the difference between normal and injected animals was more pronounced in magnitude.

Morphological Assessment of Cell Subpopulations

Smears were made from spleen and lymph node suspensions and whole blood, stained with Romanovsky's reagent, and the percentages of different classes of leucocytes determined. Only a small percentage of nonlymphocytes were observed in the smears made from lymph node and spleen cells. Cell counts made from animals injected with BDR/CFA or with saline/CFA did not differ from uninjected controls. Blood from normal animals contained 77 ± 8 per cent (mean ± SD) lymphocytes, 15 ± 3 per cent polymorphonuclear leucocytes, 8 ± 6 per cent macrophages, 0.2 ± 0.3 per cent eosinophils and 0.1 ± 0.2 per cent basophils. There was a slight tendency for the percentage of lymphocytes to be low and the percentage of polymorphs to be high during the early stages of EAN (samples taken on days 5 and 8), but this was not significant. No other consistent differences were observed.

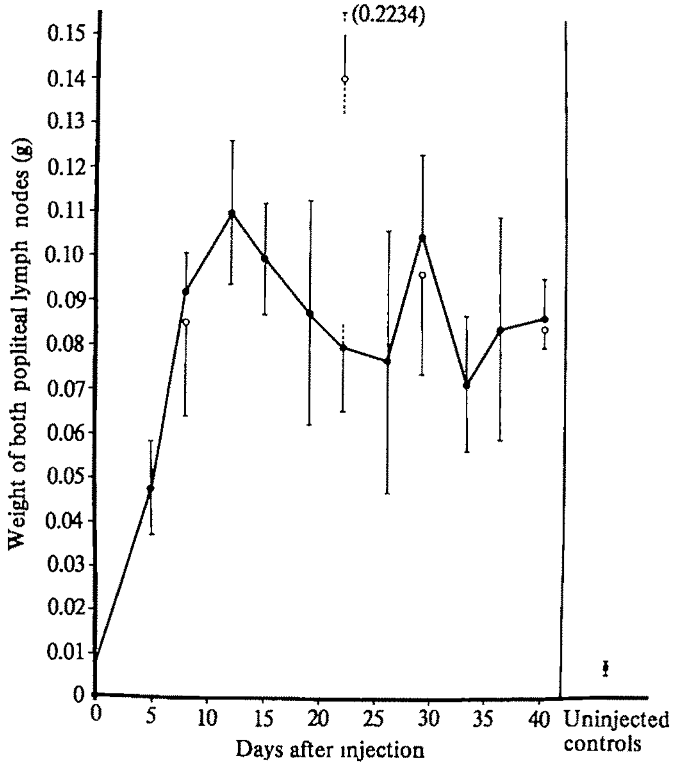

FIG. 2. Weights of popliteal lymph nodes. In this and all subsequent figures, n = 2 for rats injected with saline/CFA; n = 3 for rats injected with BDR/CFA and killed at day 36; n = 4 for rats injected with BDR/CFA and killed at all other times; n = 8 for normal uninjected rats. ●——● Injected with BDR/CFA; ○ injected with saline/CFA; ⊗ uninjected.

Cell Subsets as Defined by Surface Antigen Labelling with Antibodies

Aliquots of leucocytes from the spleen, popliteal lymph nodes and blood were made and stained to detect surface Ig+, W3.13+, W3.25+, OX 8+ and OX 3+ cells (*see* Table 2). The percentage of cells labelled with each antibody was determined for all cells, for lymphocytes alone, and for cells with greater forward and/or 90 deg scatter than lymphocytes. Lymphocytes formed the majority of cells from each organ and results from total cells therefore resembled those from lymphocytes alone. Nonlymphocytes tended to show high background fluorescence. Some cells were autofluorescent and many labelled with the second stage fluorescent antibody, SAM-FITC, reflecting nonspecific antibody binding. These cells were therefore difficult to analyse since small changes in percentages of specifically labelled cells would be masked by nonspecific background fluorescence. No gross differences were observed between nonlymphocytes from any of the tissues in any of the groups of rats examined. Only the results from the lymphocytes are therefore presented below.

TABLE 5. PERCENTAGES OF VARIOUS SUBSETS IN LYMPHOCYTES OF NORMAL LEWIS RATS[a]

	Blood	*Spleen*	*Lymph node*
Surface Ig^+	21.8 ± 5.0[b]	38.1 ± 4.5	28.3 ± 4.9
OX 3^+	18.2 ± 4.1	36.4 ± 5.2	26.7 ± 4.7
$W3.13^+$	72.9 ± 5.6	54.7 ± 4.4	63.5 ± 3.5
$W3.25^+$	54.3 ± 4.1	40.8 ± 5.8	55.2 ± 4.0
OX 8^+	22.8 ± 2.5	17.5 ± 1.8	15.9 ± 2.2
Ratio			
$W3.25^+$/OX 8^+	2.40 ± 0.28	2.36 ± 0.28	3.54 ± 0.59

[a] Single cell suspensions from lymph node, spleen and blood from individual normal control rats were labelled as described in Methods. Cells with the scatter characteristics of lymphocytes were analysed on a cytofluorograph to determine the percentage of cells in each subset as defined by the antibodies used. [b] The results are expressed as mean ± SD for 8 rats.

The data obtained from the normal rats are shown in Table 5. The percentages of surface Ig^+ and $W3.13^+$ cells did not add up to 100 per cent in any of the tissues; a small population of null cells (surface Ig^- $W3.13^-$) was therefore present in the cells analysed. The percentage of OX 3^+ cells was always slightly less than the percentage of surface Ig^+ cells. The percentages of $W3.25^+$ and OX 8^+ cells added up to just over the percentage of $W3.13^+$ cells in all the tissues despite the fact that in mature peripheral T cells $W3.25^+$ and OX 8^+ cells were originally considered to be nonoverlapping subsets contained within and filling the $W3.13^+$ subset (Brideau *et al.*, 1980). The discrepancy observed was not due to cell clumping since single cell suspensions made by running the cells through a narrow gauge needle immediately before analysis gave the same result. No attempt was made to see if any subsets overlapped and so it is not known if the results were due to the presence of $W3.25^+$ OX 8^+, $W3.13^-$ $W3.25^+$ or $W3.13^-$ OX 8^+ cells. There is evidence for the existence of each of these types of cells. $W3.25^+$ OX 8^+ cells have been found in antigen-primed rats (Spickett and Mason, 1983). $W3.13^-$ $W3.25^+$ macrophages (Barclay, 1981) and $W3.13^-$ OX 8^+ natural killer cells (Cantrell *et al.*, 1982) have been observed. In this study most macrophages and large natural killer cells should have been excluded from analysis on the basis of their light scattering properties.

Analysis of the blood lymphocytes from animals with EAN and adjuvant controls showed that there was no significant difference in the percentages of cells labelled for surface Ig, OX 3, W3.13 (data not shown) or W3.25 (fig. 3). There was, however, a significant drop in the percentage of OX 8^+ cells in animals with EAN on days 19 and 22 (fig. 3). The 95 per cent confidence limits for the percentage of OX 8^+ cells in normal rat blood were 21.1 to 24.5. The percentages of OX 8^+ cells in the

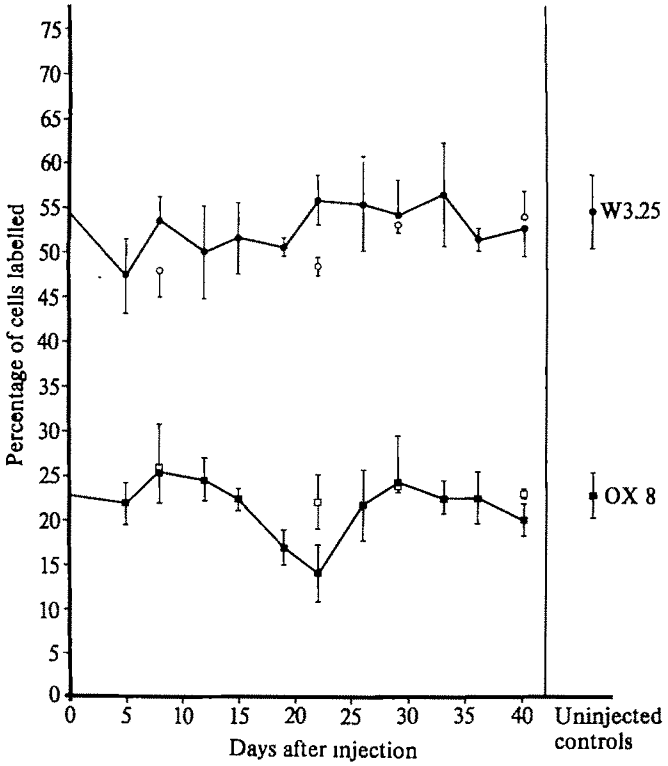

FIG. 3. Percentages of W3.25$^+$ and OX 8$^+$ cells in blood lymphocytes. ●——● Injected with BDR/CFA, % W3.25$^+$; ■——■ injected with BDR/CFA, % OX 8$^+$; ○ injected with saline/CFA, % W3.25$^+$; □ injected with saline/CFA, % OX 8$^+$; ⊗ uninjected, % W3.25$^+$; ⊠ uninjected, % OX 8$^+$.

EAN rats on day 19 were 15.0, 16.7, 16.7 and 19.7 and on day 22 were 12.2, 14.2, 15.2 and 16.7. Adjuvant controls showed no significant changes in the percentage of OX 8$^+$ cells. The W3.25$^+$/OX 8$^+$ cell ratio was correspondingly raised in animals with EAN on days 19 and 22 (fig. 4), most of which was accounted for by the change in percentage of OX 8$^+$ cells. The 95 per cent confidence limits for the ratio in normal rat blood were 2.2 to 2.6. In EAN rats the ratios on day 19 were 2.6, 3.0, 3.0 and 3.5; on day 22 they were 3.5, 4.1, 4.1 and 4.3. It should be stressed that these results were obtained in two separate experiments.

In the splenic lymphocytes from animals with EAN, there was a slight tendency for the percentage of OX 8$^+$ cells to be decreased (fig. 5) and the W3.25$^+$/OX 8$^+$ cell ratio to be raised (fig. 6) over the values of normal controls on days 19 and 22 but this was not statistically significant and there were no significant changes in any of the other subsets. Adjuvant controls showed no deviation from normal at any time in any of the subsets.

In the popliteal lymph nodes both from the animals with EAN and the adjuvant

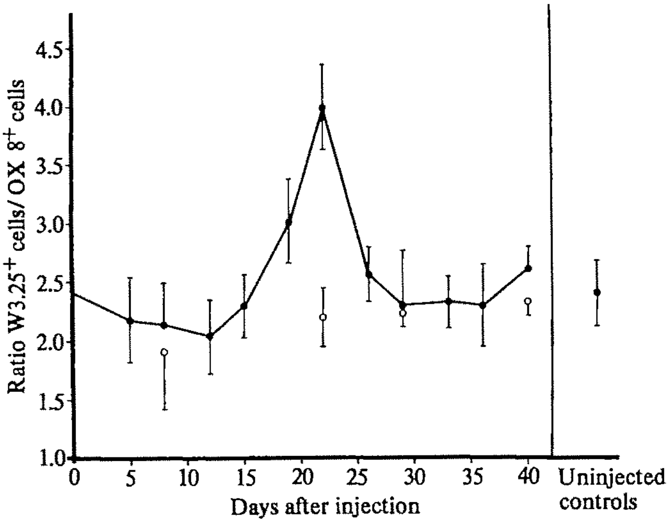

FIG. 4. The ratio of W3.25⁺/OX 8⁺ cells in blood lymphocytes. ●——● Injected with BDR/CFA; ○ injected with saline/CFA; ⊗ uninjected.

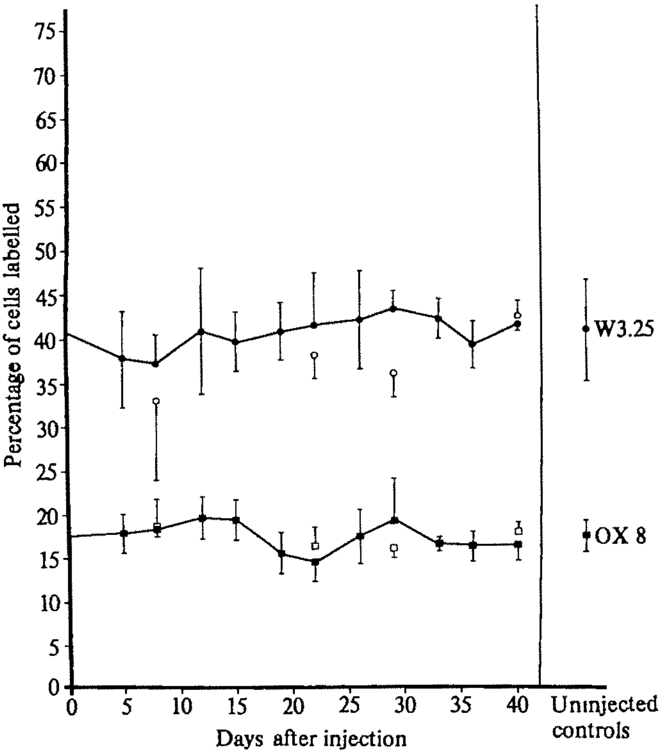

FIG. 5. Percentages of W3.25⁺ and OX 8⁺ cells in splenic lymphocytes. ●——● Injected with BDR/CFA, % W3.25⁺; ■——■ injected with BDR/CFA, % OX 8⁺; ○ injected with saline/CFA, % W3.25⁺; □ injected with saline/CFA, % OX 8⁺, ⊗ uninjected, % W3.25⁺; ⊠ uninjected, % OX 8⁺.

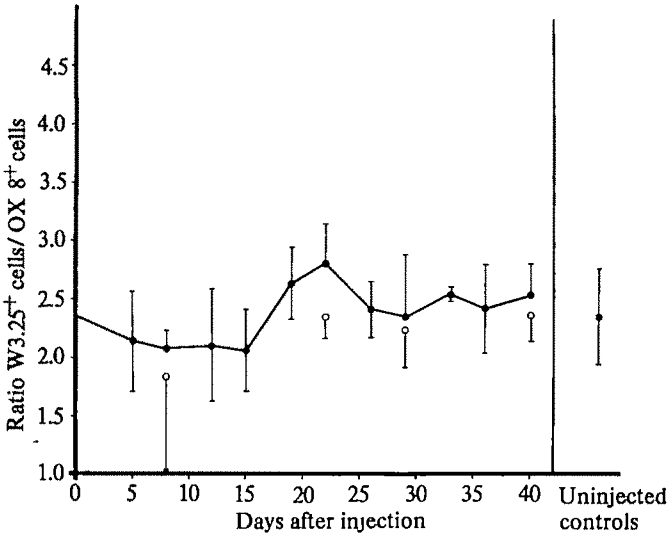

FIG. 6. The ratio of W3 25+/OX 8+ cells in splenic lymphocytes. ●——● Injected with BDR/CFA; o injected with saline/CFA; ⊗ uninjected.

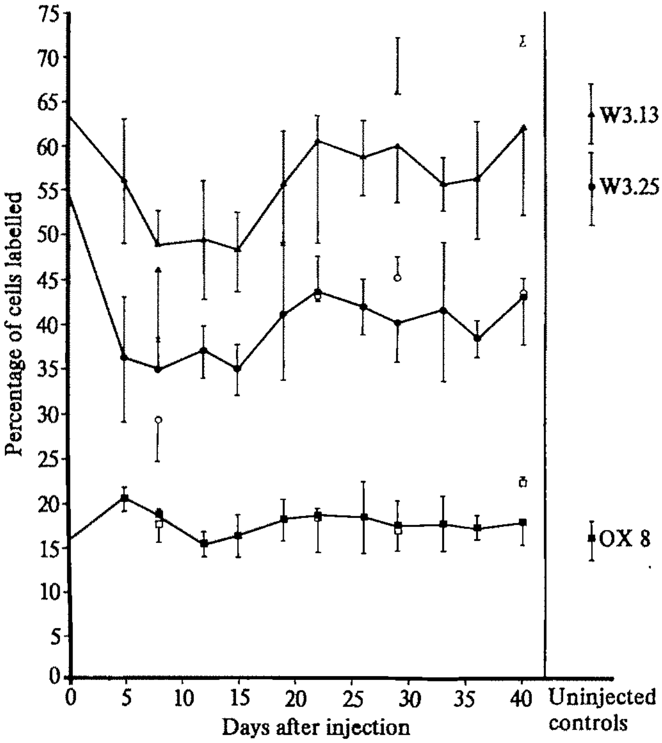

FIG. 7. Percentages of W3.13+, W3.25+ and OX 8+ cells in lymphocytes from popliteal lymph nodes. ▲——▲ Injected with BDR/CFA, % W3.13+; ●——● injected with BDR/CFA, % W3.25+; ■——■ injected with BDR/CFA, % OX 8+; ▵ injected with saline/CFA, % W3.13+; o injected with saline/CFA, % W3.25+; □ injected with saline/CFA, % OX 8+; ⚠ uninjected, % W3.13+; ⊗ uninjected, % W3.25+; ⊠ uninjected, % OX 8+.

controls, the percentages of surface Ig$^+$ and OX 3$^+$ cells were not significantly different from the normal control values (not shown). The percentages of W3.13$^+$ cells did not change significantly, although adjuvant controls and animals with EAN tended to have subnormal numbers at most times examined (fig. 7). This was mainly due to a drop in the percentage of W3.25$^+$ cells, with the percentages of OX 8$^+$ cells remaining the same as in normal animals (fig. 7). The W3.25$^+$/OX 8$^+$ cell ratio was therefore depressed in adjuvant controls and animals with EAN (fig. 8). The ratio was particularly low on days 5 and 8, but there was no other obvious trend with time after injection. It should be noted that these changes in the lymph nodes, unlike those in the blood, applied equally well to animals with EAN and to adjuvant controls, and were therefore not specific to the disease.

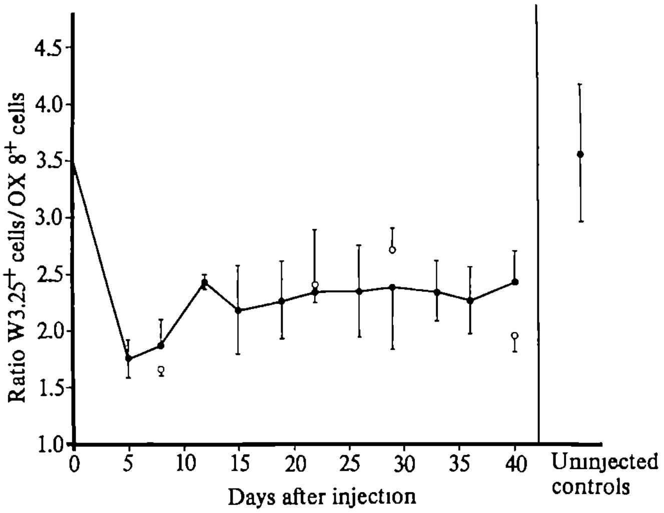

FIG. 8. The ratio of W3.25$^+$/OX 8$^+$ cells in lymphocytes from popliteal lymph nodes. ●——● Injected with BDR/CFA; o injected with saline/CFA; ⊗ uninjected.

DISCUSSION

The most important result in this study was the significant decrease in the percentage of OX 8$^+$ cells in the blood observed at days 19 and 22 after injection of BDR/CFA. This change was disease specific since it was not produced by the injection of adjuvant alone. There was no accompanying increase in the percentage of any other subset, including null (W3.13$^-$ surface Ig$^-$) cells (data not shown), but minor perturbations within the other subsets could have occurred without reaching significance due to individual variability. There was no significant change in the absolute numbers of blood lymphocytes, but again minor variations could have been masked. No attempt was made here to study overlaps between OX 8$^+$ cells and other subsets, so that any variation in this respect is unknown.

Clinical and histological signs of disease were very well correlated. They commenced together and histological evidence of ongoing activity, that is demyelination and cell infiltration, was most marked when clinical disease was most severe (days 19–22), while evidence of remyelination paralleled the clinical recovery. The drop in percentage of OX 8^+ cells coincided with the period when the animals were most severely affected (fig. 1 and Table 4). At day 19 the animals had, on average, just reached their maximum grade, and at day 22 they had not significantly improved (Table 3). This suggests that the change in OX 8^+ cells may just precede the start of recovery and may be linked to this event. A number of possible explanations could connect the decrease in blood-borne OX 8^+ cells with the onset of recovery from EAN.

First, the OX 8^+ cells have been shown to contain suppressor T cells (Brideau *et al.*, 1980). One possibility is that suppressor cells are recruited away from the circulating pool to areas of active disease (in this case peripheral nerves) where they could prevent further immune reaction and thus allow recovery. A decrease in the percentage of rapidly rosetting T cells in the blood in EAE in guinea pigs has been shown to be accompanied by an increase in the percentage of the same subset in cerebrospinal fluid (Traugott *et al.*, 1978) showing that redistribution of cells can occur on a gross scale in autoimmune nervous disease. It is interesting that in the present study a generalized decrease in the percentage of OX 8^+ cells was not observed: levels in the lymph nodes remained constant and in the spleen nearly constant, an observation that may be accounted for by the fact that some cells in these organs do not recirculate (McGregor and Gowans, 1963) and by differential homing properties of individual lymphocytes (Gallatin *et al.*, 1983). The slight depression of OX 8^+ cells in the spleen was almost certainly due to blood-borne cells.

Cytotoxic T cells and some natural killer cells are also contained within the OX 8^+ cells (Cantrell *et al.*, 1982; Dallman *et al.*, 1982). It is not known whether killer activity plays a direct role in EAN. If it does, then a decrease in blood-borne OX 8^+ cells may reflect a more generalized decrease in cytotoxic response, including that within the nerves themselves. If cytotoxicity, mediated by antigen-specific T cells, natural killer cells, or antibody-dependent cytotoxic cells, is responsible for demyelination then cessation of this activity would allow remyelination and clinical recovery.

The monoclonal antibodies OX 8 and W3.25 in the rat and their analogues in man and the mouse were originally thought to define T cell suppressor/cytotoxic and helper subsets, respectively. It is, however, apparent that this is not so, since each of these two major subsets of T lymphocytes has been shown to display helper and suppressor/cytotoxic function (Thomas *et al.*, 1981; Thomas and Calderon, 1982). It was later proposed that the subset originally defined as 'helper' was involved in interactions involving Class II major histocompatibility antigens, and the subset originally defined as 'suppressor/cytotoxic' concerned with interactions with Class I antigens (Meuer *et al.*, 1982) but even this distinction may not hold (Pawelec *et al.*, 1982) and the phenotype of cells as defined by monoclonal antibodies may not be stable (Thomas and Calderon, 1982). These new observations throw considerable doubt as to the function of subsets of lymphocytes distinguished by their surface antigens. It would therefore be premature to place too much emphasis on the putative suppressor or cytotoxic activity of the OX 8^+ subset in considering how the percentage of these cells in the blood during EAN may correlate with disease activity. In addition to this caveat, there may be other as yet unconsidered or unknown factors which operate during EAN, causing a simultaneous change in the percentage of OX 8^+ cells and disease status. Another possibility is that the drop in percentage of OX 8^+ lymphocytes in the blood is caused by modulation of the OX 8 antigen and not actual loss of cells.

A feature of EAN is the cellular infiltrate in the nerves (Ballin and Thomas, 1969; Lampert, 1969) and a preliminary study has shown that these cells include lymphocytes which stain with W3.13, W3.25 and OX 8 antibodies (Olsson *et al.*, 1983). It would be interesting to know, therefore, if the percentage of the various subsets change within the nerve itself during the course of EAN and studies to investigate this are planned.

Feasby *et al.* (1984) have conducted a similar study of cell subsets in the blood of Lewis rats with EAN. They did not find statistically significant alterations in any subset. Examination of their data, however, does reveal a decrease in the percentage of OX 8^+ cells (with a corresponding increase in the W3.25^+/OX 8^+ cell ratio) just before the peak of clinical disease, which occurred at day 15. This result is very similar to the observations reported here. Their study is less extensive and one possible reason for the differences in the results is that their subset analyses were on repeatedly bled rats. It is quite feasible that bleeding itself can perturb the numbers of cells in different subsets, thereby partially masking disease-related changes.

Hughes *et al.* (1983) have reported changes in blood lymphocyte subsets in the Guillain-Barré syndrome in man, for which EAN is a possible model. In some respects these results are similar to those reported here. These authors also observed no change in the percentage of OKT3^+ (total T) cells, B cells or OKT4^+ cells (OKT4 is the human analogue of W3.25). The percentage of OKT8^+ cells (the human analogue of OX 8^+ cells) was reduced in the patients, resulting in high OKT4^+/OKT8^+ cell ratios. The ratios returned to normal values in patients who had substantially recovered. However, there were no data available on patients with early disease during worsening of symptoms.

Extensive studies on subsets have been conducted in multiple sclerosis (MS), which is also believed to have a basis in altered immune reactions and pathologically it is again characterized by cellular infiltration and demyelination. Several workers have observed a decrease during acute disease in the percentage of the blood lymphocytes labelled by OKT8 or equivalent markers (Reinherz *et al.*, 1980; Compston, 1983; Hauser *et al.*, 1983; Sandberg-Wollheim, 1983).

Compston (1983) has studied several patients with MS over a period of time. His results show that where relapses have occurred, the percentage of OKT8^+ cells in the sample taken immediately before relapse was usually normal, but low in the sample taken immediately after relapse. This pattern of change is actually very close to that seen in this study and suggests that the relapse itself may sometimes occur without antecedent changes in the OKT8$^+$ subset but that recovery is preceded by a transient drop in the percentage of these cells.

A decrease in the percentage of the OKT8$^+$ subset in the blood is a common finding in autoimmune diseases (Morimoto *et al.*, 1980; Bach and Bach, 1981; Fox *et al.*, 1982). Yet it is unlikely that there is a high percentage of cells specific for the relevant antigens in EAN or other immune diseases, since the frequency of cells responding to antigens other than the major histocompatibility antigens is usually low (Kennedy *et al.*, 1966; Armstrong and Diener, 1969). Unless self-reactivity is different from the response to foreign antigens, it is therefore surprising to find measurable changes in the percentage of cells in a particular subset, and this is presumably not all due to antigen-specific cells. Autoimmune diseases are often characterized either by complete recovery from a single acute attack or by periods of remission. In EAE recovery has been shown to be associated with the activation of specific suppressor cells (Welch *et al.*, 1980). In view of all these findings it seems possible that a general, probably nonspecific, perturbation in the immune system and the spontaneous occurrence of suppression of autoimmunity are linked.

The blood samples from animals with EAN showed no significant changes in the total white cell count, the percentages of morphologically differentiated leucocytes or the percentage of surface Ig$^+$, Ia$^+$, W3.13$^+$ or W3.25$^+$ lymphocytes. This is consistent with some studies of other autoimmune diseases including EAE (Traugott *et al.*, 1978), MS (Weiner and Schocket, 1979; Kam-Hansen, 1980; Compston, 1983) and the Guillain-Barré syndrome (Hughes *et al.*, 1983) although some investigators have found a decrease in the percentage of total T cells and OKT4$^+$ cells (Lisak *et al.*, 1975; Reinherz *et al.*, 1980; Sandberg-Wollheim, 1983) and, occasionally, an increase in the percentage of B cells in the blood (Lisak *et al.*, 1975; Oger *et al.*, 1975) particularly during acute disease. Therefore changes in the percentages of OKT8$^+$ and OX 8$^+$ subsets predominated in this investigation and in the studies discussed above.

No significant differences were found in the spleen in any of the parameters examined, that is in the organ weights, cell yields or cell subset percentages. The minor tendency for the percentage of OX 8$^+$ cells to decrease during the peak of the disease probably reflected the changes in blood-borne cells.

The popliteal lymph node enlarged similarly in both adjuvant and BDR/CFA immunized animals, presumably due to a generalized antigen/adjuvant stimulation. There was a tendency for the percentage of W3.13$^+$ cells to be decreased (fig. 7) and null cells (W3.13$^-$ surface Ig$^-$) to be increased (data not shown) at all times after injection and a decrease in the percentage of W3.25$^+$ cells occurred in most of the injected animals (fig. 7). No changes unique to EAN animals were observed in the lymph nodes, showing that there was no gross disease-related immunological imbalance in this tissue although it drains the injection site. As only recirculating cells can reach the nerve where the autoimmune process occurs, it is perhaps not surprising that disease-specific changes were found only in the blood and not the lymphoid organs which also contain cells which do not recirculate or which recirculate only slowly (McGregor and Gowans, 1963).

It can be concluded from this study that a decrease occurs in the percentage of OX 8^+ cells in the blood of animals with EAN at the peak of disease, just before the start of recovery. The percentage returns to normal during the early period of clinical recovery. No such changes occur in the popliteal lymph nodes and are minor, if present at all, in the spleen. No significant changes specific to disease occurred in cell numbers, organ weights or in the percentages of morphologically differentiated leucocytes or of B cells, Ia^+, $W3.13^+$ or $W3.25^+$ lymphocytes in the blood, spleen or lymph nodes during disease or recovery. Changes in the percentages of the subset defined by OX 8 antibody in the rat and OKT8 antibody in man seem to be a common occurrence in autoimmune diseases. It seems likely that this reflects a generalized imbalance in the immune system, a phenomenon which could be related to the initial self-reactivity and the emergence of suppression despite the continued presence of self-antigen.

ACKNOWLEDGEMENTS

We are most grateful to M. Aristidou, S. Bhagat, C. Feuchtwang, D. Fleming, J. A. Macquire, A. Watson and J. M. Workman for invaluable technical assistance and to the Haematology Laboratories at the Royal Free Hospital for staining the smears. Financial support from the Nuffield Foundation, the Sir Jules Thorn Charitable Trust, the National Fund for Research into Crippling Diseases and the Medical Research Council is acknowledged.

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(*Received July 7, 1984. Revised September 17, 1984. Accepted September 27, 1984*)

Brain (1985), **108**, 335–365

VISUAL FIELD RECOVERY FROM SCOTOMA IN PATIENTS WITH POSTGENICULATE DAMAGE

A REVIEW OF 55 CASES

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SUMMARY

A group of 55 patients with homonymous field defects related to vascular or traumatic postgeniculate damage were trained by locating light targets presented within their blind field region. This systematic treatment led, in the majority of patients, to an enlargement of the visual field. Recovery depended on specific practice. Control experiments showed that field enlargement cannot be explained by eccentric fixation or perimetric measurement variability.

It is hypothesized that recovery may take place at striate cortex level and may result from 'reactivation' of reversibly damaged nervous tissue. In cases that did not benefit from treatment, visual field loss may result from irreversible damage.

INTRODUCTION

It has long been established that visual fields can recover from scotoma in patients with damage to the geniculostriate pathway after cerebral infarction or gunshot injuries (*see* Zagórski, 1867; Poppelreuter, 1917; Riddoch, 1917; Wilbrand and Saenger, 1917; Hine, 1918). Patients with homonymous field defects from vascular disease seem to have a generally poor prognosis for spontaneous recovery (Lenz, 1905; Wilbrand and Saenger, 1917), even though some improvement may be observed within a relatively short period of time after the occurrence of cerebral damage (within 48 h: Haerer, 1973; within at least two weeks: Gloning *et al.*, 1962). In contrast, patients with traumatic damage (mostly due to gunshot wounds) very often showed remarkable visual field recovery from scotoma (*see* Poppelreuter, 1917; Hine, 1918; Teuber *et al.*, 1960). In these cases, however, recovery was often restricted to light perception, recovered field regions showing sensory instability (Poppelreuter, 1917; Bender and Teuber, 1946). These reports were in agreement that permanent, cerebral blindness, whether total or partial, has to be attributed to

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irreversible brain damage, while recovery can be observed only in those field regions in which vision was transiently lost after reversible impairment of cerebral functioning (Wilbrand and Saenger, 1917; Holmes, 1918; Haerer, 1973).

While spontaneous recovery from cerebral blindness has been reported by several authors, systematic attempts to restore visual function were not made except by Poppelreuter (1917) and later by Preobrazhenskaya (cited by Luria, 1963). Poppelreuter trained hemianopic patients mainly in reading, since patients with visual field loss near the fovea usually exhibit particular difficulties for this activity ('hemianopic dyslexia': Wilbrand, 1907). After systematic treatment he found a markedly improved reading performance. Unfortunately he did not measure the visual fields before and after training. Preobrazhenskaya treated hemianopic patients in a similar way, as did Poppelreuter. She reported an improvement in reading performance from an enlargement of the perifoveal visual field, as verified by perimetric field testing, but did not specify the amount of the field enlargement.

The assumption that visual function can recover after cerebral damage has been supported by experimental studies with primates after striate cortex lesions. These showed that detection and localization of light stimuli can be restored by systematic training. The observed recovery from scotoma did not occur spontaneously, indicating that the improvement resulted from specific practice (Cowey and Weiskrantz, 1963). Furthermore, recovery was most prominent in the field region subjected to treatment and was therefore not a general effect occurring within the whole scotomatous region (Mohler and Wurtz, 1977).

In this paper we present experimental data and observations on 55 patients, all trained using saccadic localization of light stimuli (*see* Zihl, 1981). The essential aim of this investigation was to establish how frequently and to what extent recovery could be observed in patients with postgeniculate damage, either after infarction in the territory of the posterior cerebral arteries or after closed head trauma. Furthermore, we were interested in discovering what role 'patient variables' such as age and sex, and 'damage variables' (e.g. time after lesion, size of visual field loss, side and severity of cerebral damage and aetiology of lesion) may play in visual field recovery. Further, patients' reports concerning their disabilities from visual field loss, especially with regard to reading, were analysed before and after treatment. Finally, a number of control experiments were undertaken in order to exclude various artefacts which could possibly partly explain the results, or even distort their interpretation.

PATIENTS

The group of 55 patients studied represent a *post hoc* sample out of a larger group (n = 125) participating in this investigation. Selection of patients reported here was based on complete availability of perimetric and computer-tomographic data, but not on treatment effects. The patients demonstrated no neuropsychological deficits (aphasic or memory disorders) which could interfere with treatment. Details of the 55 patients are given in Table 1. Six of the patients reported here were described in an earlier study (Zihl, 1981: Cases 1-6).

TABLE I. CLINICAL DETAILS OF PATIENTS

A. Age	*(yrs)*	*< 20*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*> 70*
	A	00	07	02	12	15	07	01
	B	02	02	03	03	01	00	00

B. Sex Females A: 18 B: 03 Males A: 26 B: 08

C. Side of damage Left A: 31 B: 06 Right A: 13 B: 05

D. Time since first evidence of homonymous field loss and beginning of visual training

Months	*1*	*2*	*> 3*
A	7	16	21
B	1	02	08

A: patients with posterior cerebral artery infarction (n = 44; 80%). B: patients with closed head injury (n = 11; 20%).

Most patients (80%) had sustained infarction in the territory of the left (13 cases; 29.5%) or right posterior cerebral artery (31 cases or 70.5%). The imbalance between the numbers with left- and right-sided lesions was due to the selection criteria. Since patients with aphasia were not accepted, the number of the patients with right-sided damage is much higher. In the total group of 125 patients, the distribution was more balanced (44% patients with left-sided, and 56% with right-sided damage). Eleven patients (20%) had sustained a closed head injury, in 7 of these from a road traffic accident and in 4 from an accident at their place of work. No patient of this group showed a hypodense area affecting the postchiasmatic visual pathway on CT scanning. In contrast, all patients with infarction showed clear signs of a structural lesion evidenced by CT hypodensity. Signs typical of an optic tract hemianopia were not present in either group (*see* Savino *et al.*, 1978), indicating that damage had most probably occurred at a postgeniculate site.

The time interval from the first evidence of the homonymous field loss to the beginning of treatment varied from 4 wks to 2 yrs 4 months. In all cases, the visual fields were first tested within 2 wks of the occurrence of brain damage except in one case, who had sustained closed head trauma, in whom perimetry was first performed 25 days afterwards. Oculomotor performance (fixation, saccadic eye movements) was normal in all cases and no obvious ophthalmological disorder was detected. Decimal near acuity (corrected) was 1.00 in 40 patients (73%), 0.80 in 12 (22%) and 0.67 in 3 (5%).

The main problems of which the patients complained were difficulty in reading ('hemianopic dyslexia'; *see* p. 348) and in avoiding obstacles or people on the side of their field defect. All patients were interviewed in a semistandardized manner, before and after training, concerning these disabilities, as detailed later.

METHODS

Perimetry

The visual fields were mapped by dynamic (kinetic) and static perimetry using a modified Tübinger perimeter. The perimeter was the same as the standard model (*see* Aulhorn and Harms, 1972) except that the spatial resolution up to the inner 15 deg eccentricity was at least 15 min of arc visual angle (*see* section on Controls in Results). If not indicated otherwise, target luminance was 102 cd/m^2 and background luminance 3.2 cd/m^2 in all testing conditions. Eye position was monitored using an infrared camera and a monitor; head position was maintained by a chin rest. During visual field mapping, the patients fixated on a red spot of light (30 min of visual angle in diameter) in the centre of the sphere at a distance of 33 cm.

For dynamic perimetry, the target was moved with a constant velocity of about 2 deg/s from the periphery towards the centre of the sphere. Target diameter was 116 min visual angle for the field outside 15 deg eccentricity, and 27 min visual angle for the field within 15 deg eccentricity. The patients were instructed to maintain fixation and to press a buzzer key whenever they detected the appearance of the test target. The extent of the visual field was determined for 16 meridians, randomly, under monocular and binocular viewing conditions. Perimetric trials in which the patient did not maintain fixation were excluded (this was also true for the following perimetric examinations).

The profile of light sensitivity was determined by means of static perimetry under binocular viewing conditions. Light difference thresholds were measured using the method of ascending limits. The target had a diameter of 69 min of visual angle and was presented for 500 ms. Its luminance was initially well below threshold and was then increased in steps of 0.05 log units. When the patients detected three targets consecutively, the luminance of the first of these was defined as threshold.

Recognition of colour and form was tested by mapping the binocular visual field for colours and forms. The coloured targets (blue: 480 nm; green: 525 nm; red: 656 nm) had a diameter of 116 min visual angle and were presented with maximum intensity (320 cd/m^2). Each target was shown to the patients before plotting the visual field for that colour by dynamic perimetry (*see above*). The patients were asked to press the buzzer key whenever they were able to identify the hue of the target (*see* Carlow *et al.*, 1976; Zihl and Mayer, 1981). Form fields were measured binocularly using the different sizes of the diamond available in the Tübinger perimeter, and were moved at about 1 deg/s from the periphery to the centre of the perimeter. The patients were asked to press the buzzer key when they were able to identify the form of the target. In addition, the profile of binocular visual acuity was determined along a given meridian, usually along the horizontal axis, using profile perimetry (*see* Johnson *et al.*, 1979). The test stimuli included seven different sizes of circle and diamond pairs, ranging from 7 min visual angle in diameter (equivalent to 20/20 Snellen acuity, or 1.00 decimal acuity) to 116 min visual angle (20/330 Snellen acuity, or 0.06 decimal acuity). Targets were presented for 500 ms. Each size of the circle and the diamond were presented three times with a random sequence. The patient was instructed to report which target (circle or diamond) was presented. Errorless performance was chosen as a criterion for accurate form discrimination.

Detection performance in both hemifields was tested tachistoscopically using a simultaneous double stimulation technique (*see* Zihl and von Cramon, 1979*a*). Light targets were presented simultaneously in the intact and affected hemifield at corresponding positions (e.g. in cases of hemianopia along the horizontal axis and 10 deg above or below the horizontal axis in the upper and lower quadrants). Target diameter was 30 min visual angle, luminance 1.3 cd/m^2 (contrast ratio to uniform background 13:1) and presentation time 10 ms. Twenty trials were conducted with each patient; intertrial interval varied between 5 and 8 s. In addition, trials with unilaterally presented targets (5 in both hemifields) were interspersed randomly with test trials (bilateral simultaneous presentation) in order to reveal any response bias. The patients were asked to fixate on a red spot of light (as the 0 deg position) and to report whether they saw one or two stimuli. They were not allowed to make head movements and were not informed about the 'catch' trials.

Recognition of visual stimuli was tested by binocular tachistoscopic presentation of 10 black painted numerals, arranged in a random sequence and presented on a white projection screen. Stimuli were again presented along the horizontal axis or about 10 deg above or below it in the upper or lower quadrants, starting at the vertical axis and reaching into the left and right hemifields. Stimulus height was 5.7 deg visual angle, and distance between numerals was adjusted to 1 deg visual angle at a viewing distance of 120 cm. Presentation time was 80 ms which is well below saccadic response time (*see* Frost and Pöppel, 1976). The numerals were presented randomly either in the left or right hemifield. Ten trials were performed for each condition. The patients were asked to report how many numerals they had recognized, but were not informed as to the side of presentation nor the number of numerals presented.

Training Procedure

Visual training, based on saccadic localization of targets presented within the scotomatous region, was performed with the Tübinger perimeter and has been described in detail elsewhere (*see* Zihl, 1981). Briefly, the patient was asked to shift his eyes with one sweep at the onset of an acoustic signal from the centre of the sphere, that is, the fixation point, towards the scotomatous side where the light targets were presented for 1 s at different positions randomly between 10 and 40 deg eccentricity along one meridian. The patients were informed along which meridian light targets would be presented. They were never told, however, about the positions of the targets or the order of presentation.

Training sessions were performed either daily or at least three times a week. In any session, between 80 and 120 trials were conducted. Patients were never informed as to the outcome of the training sessions.

Enlargement of the field of 1.5 deg visual angle was accepted as an increase since this amount differed highly significantly from the error of perimetric measurement in our testing conditions (*see* section on Accuracy and Reliability of Perimetric Testing).

In about half of the cases (24 patients), periods without training were introduced (range: one to six weeks) in order to evaluate the effect of treatment on visual field recovery from scotoma. Furthermore, the visual field was followed up for at least four months and, in some cases, even for two years, in order to investigate whether the field region recovered from scotoma had undergone any changes.

RESULTS

Visual Field Data before Training

The extent of the visual field on the affected side varied between 1.5 and 26 deg eccentricity. In cases with a left or right homonymous hemianopia (44 patients or 80%), this residual field is referred to the horizontal axis. In the rest of the group (11, or 20%), the field border refers to the oblique meridians (homonymous quadrantanopia; 45, 135, 225 and 315 deg meridians).

Eight (14.5%) patients showed less than 2 deg residual field, 27 (49.1%) possessed a residual field ranging from 2 to 4.5 deg, 15 patients (27.3%) between 5 and 10 deg, and 5 patients (9.1%) showed a residual field larger than 10 deg visual angle. Most of the patients (35, or 63.6%) showed a residual visual field of less than 4.5 deg, indicating that macular sparing (as defined by Putnam and Liebman, 1942) was the exception rather than the rule. The degree of the residual visual field on the affected side did not depend on the age of the lesion (Spearman correlation coefficient, used also for all following correlations, $r = 0.02$; $P > 0.40$), nor on patients' age at time of cerebral damage ($r = -0.15$; $P > 0.10$), nor on the side of the cerebral damage ($r = -0.06$; $P > 0.30$).

Spontaneous recovery was seldom observed. The overwhelming majority of cases (51, or 92.7%) did not show any significant change in field border in the time period between the first evaluation of the homonymous field loss and the first perimetric control—an interval of at least three weeks (t test: $P > 0.50$; two-tailed for this and all following t tests). Only in 4 patients (7.3%) was some spontaneous recovery observed (2 deg visual angle in 3 cases, and 3 deg in 1 case). During the second period, that is, the interval between the first perimetric control and the beginning of treatment which ranged from four weeks to 28 months (*see* Table 1D), the field border remained unchanged in all patients (t test: $P > 0.20$).

Effect of Treatment on the Visual Field for Light Vision

Degree of enlargement. In 44 (80%) of our patient group, an enlargement of the visual field greater than 1.5 deg visual angle was found. About half of these patients (23, or 52%) showed an increase between 1.5 and 5 deg visual angle; 7 patients (16%) between 6 and 10 deg, and 14 patients (32%) showed an increase larger than 10 deg visual angle, ranging from 10 to 48 deg. This change in the visual field border was highly significant (Wilcoxon test: $P < 0.001$) indicating a significant enlargement of the field size after training. In contrast, in 11 cases, 8 with infarction in the territory of the posterior cerebral artery and 3 with a closed head trauma, significant enlargement was not detected (t test: $P > 0.50$).

The degree of increase in visual field size was not found to correlate significantly with the sex ($r = 0.21$; $P > 0.08$) or age ($r = -0.10$; $P > 0.26$) of the patients, nor with the time from the occurrence of the lesion ($r = -0.15$; $P > 0.16$; *see* fig. 1), the side of lesion ($r = 0.13$; $P > 0.20$) or the type of cerebral damage ($r = 0.08$; $P > 0.30$). Furthermore, the increase in field size did not depend on the field axis (meridian) along which training had been performed ($r = -0.08$; $P > 0.30$).

Enlargement of visual field was never observed along the whole field border but instead was restricted to particular regions. Figs. 2 and 3 show the binocular visual field plots of 4 patients and the effect of training on recovery from scotoma. The first patient shown (fig. 2A) exhibited a nearly complete left homonymous

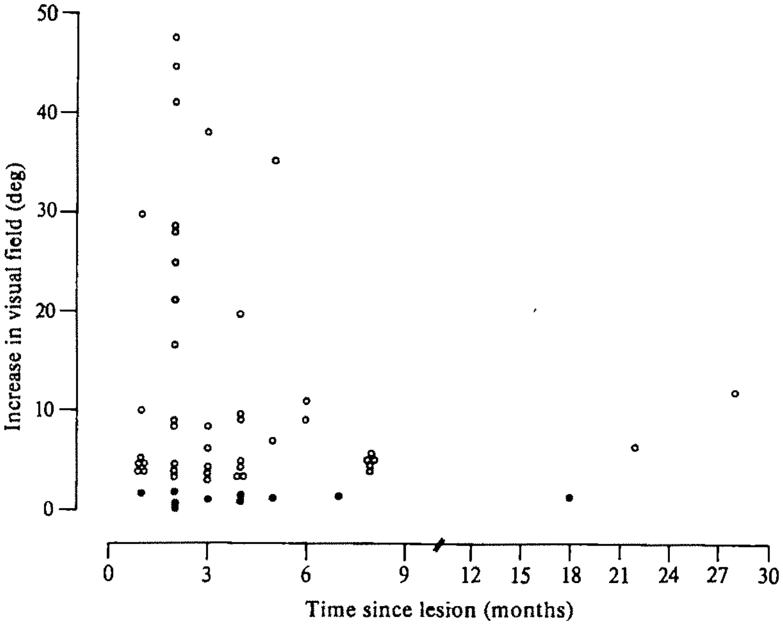

FIG. 1. Increase in binocular visual field size (in deg visual angle) as a function of time since cerebral damage ($n = 55$). Open circles = patients with field enlargement; filled circles = patients without field enlargement (< 1.5 deg visual angle).

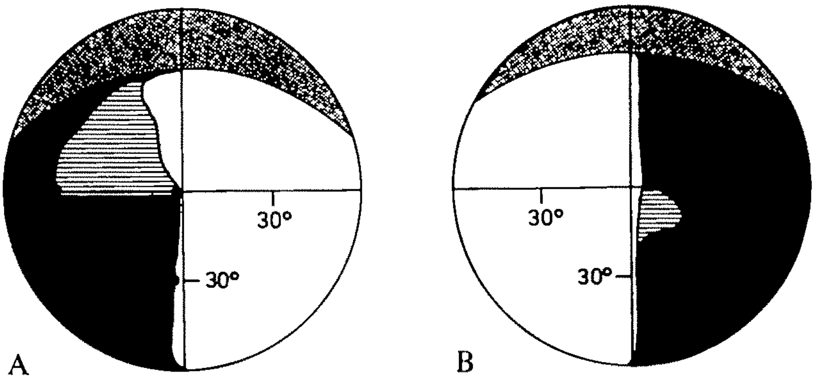

FIG. 2. Field plots from 2 patients (aged 48 and 51 years; time since cerebral infarction 4 and 6 wks, respectively) showing field enlargement after treatment. Results of binocular dynamic perimetry are shown up to 60 deg eccentricity. Hatched areas indicate the regions recovered after treatment. Note recovery limited to a particular field region within both quadrants despite training. Black dots indicate positions of perimetric control measurements (*see* p. 350). For further details *see* text.

hemianopia before training. Training was performed, first, along the 135 deg meridian in the left upper and, subsequently, along the 225 deg meridian in the left lower quadrant. After 900 trials, the left upper quadrant was almost completely restored; the first enlargement greater than 1.5 deg visual angle was observed after 60 trials. In contrast, no improvement was detected in the left lower quadrant even after 660 trials. A similar outcome was observed in another patient exhibiting a right homonymous hemianopia (fig. 2B). Training was performed, first, in the upper (along the 45 deg meridian) and, subsequently, in the lower quadrant (along the 315 deg meridian). After 840 trials no improvement was found for the right

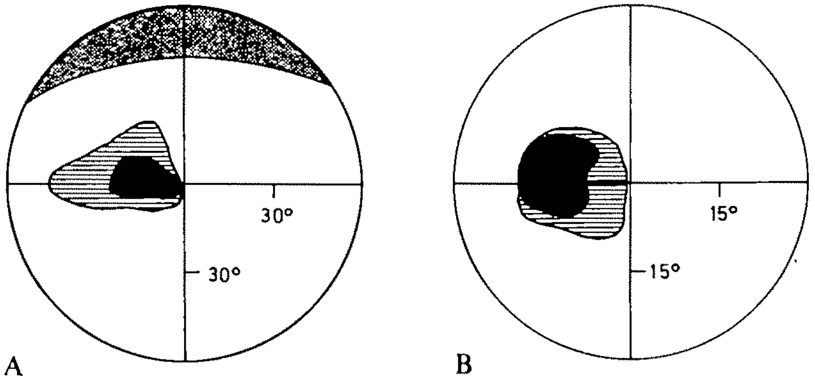

FIG. 3. Results of binocular dynamic perimetry, up to 30 deg eccentricity, in 2 patients suffering from large homonymous paracentral scotomata after posterior cerebral infarction (aged 46 and 53 years; time since lesion. A, eight weeks and B, five weeks). Hatched areas indicate recovered field regions after treatment performed along the left horizontal axis (B). Further description as in fig. 2.

upper quadrant, but an increase of 18 deg visual angle was observed along the 315 deg meridian in the right lower quadrant after 620 trials (first increase after 120 trials).

Fig. 3 shows the visual field plots of two patients exhibiting a large homonymous paracentral scotoma along the horizontal axis in the right hemifield. In the first case (fig. 3A) recovery of vision was limited to the peripheral part of the scotoma, while in the second case vision returned in the more central part (fig. 3B). Thus, in both cases, the size of the scotoma remained unaffected after training on one side but decreased on the other.

Amount of training. Table 2 shows the extent of training as related, respectively, to the mean number of saccadic responses per deg visual angle and the mean number of responses until the first enlargement was observed.

TABLE 2. EXTENT OF VISUAL TRAINING*

A. Trials/deg		*20-50*	*51-100*	*101-200*	*201-300*	*301-500*
	f	12	08	07	08	09
	%	27	18	17	18	20
B. Trials/1st enlargement		*< 100*	*100-200*	*201-300*	*301-450*	
	f	07	17	11	09	
	%	16.0	38.6	25.0	20.4	

* n = 44. A: no. of saccadic responses/deg visual field enlargement. B: no. of trials before the first increase (> 1.5 deg).

There was no significant relationship between these two variables and the sex ($r = -0.15$, $P > 0.16$; $r = -0.06$, $P > 0.34$), or age of the patients ($r = 0.05$, $P > 0.36$; $r = -0.07$, $P > 0.33$), the side of the lesion ($r = -0.25$, $P > 0.05$; $r = -0.22$, $P > 0.08$), the aetiology of the damage ($r = 0.21$, $P > 0.09$; $r = 0.23$, $P > 0.07$), or the eccentricity of the field border before training ($r = -0.20$, $P > 0.09$; $r = 0.21$, $P > 0.09$). Even the duration from the time of cerebral damage did not influence the amount of visual training significantly ($r = 0.37$, $P = 0.007$).

Training was concluded when, in at least three consecutive sessions, no further field increase was observed. Thus between 240 and 420 trials were performed after the last field enlargement. In no case was a change in field size obtained in this period and perimetric data did not differ significantly from that obtained in the session when an increase was observed for last time (Wilcoxon test: $P > 0.20$; two-tailed).

In the group of 11 patients not showing any field enlargement following visual training, between 600 and 1120 trials were performed (mean: 700 trials). Thus the extent of training was much higher than that needed in the group who did benefit from visual training in order to obtain an increase in visual field size by more than 1.5 deg (maximal 450 trials; *see* Table 2B). Despite this amount of training, the visual field did not enlarge; the perimetric results obtained after training did not differ significantly from those before training (Wilcoxon test: $P > 0.50$; two-tailed).

Fig. 4 shows an example for a patient without any treatment effect. In this case training was performed along the horizontal axis, as well as in the upper and lower quadrants (45 deg and 315 deg meridians) in the right hemifield. After 700 trials along each meridian the only field increase was 0.5 deg visual angle along the right horizontal axis. According to our criterion this enlargement was not accepted as a treatment effect.

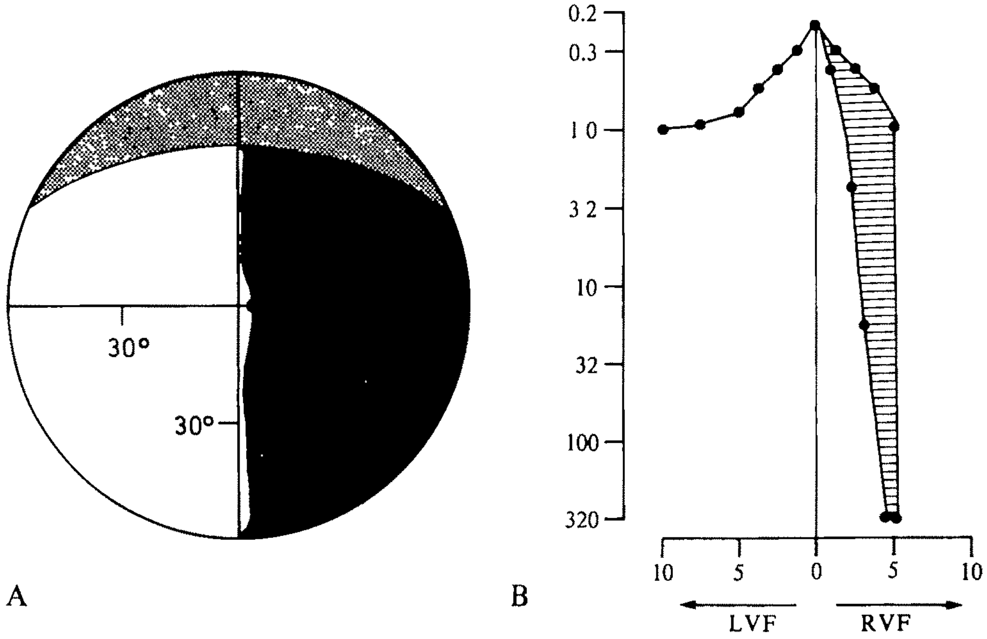

FIG. 4. Perimetric data before and after training in a 53-year-old patient, not benefiting from treatment, who had suffered posterior cerebral infarction four weeks before treatment. A, binocular visual field up to 60 deg eccentricity; B, binocular profile of light sensitivity along the horizontal axis. The hatched area indicates the region of increased light sensitivity, without any change of visual field border. LVF, RVF = left and right visual hemifield, respectively.

Dependence of recovery on periods of visual treatment. Return of vision was found to be linked to periods of visual training, as is shown in fig. 5 for 2 patients, 1 exhibiting recovery of the left upper quadrant (fig. 5A; for corresponding visual field plot, *see* fig. 2A), the other showing shrinkage in the size of the paracentral scotoma (fig. 5B; for visual field plot, *see* fig. 2A). The increase in field size in both cases was observed in periods only when training was performed. This also holds true for the other 22 patients, with a treatment-free interval ranging from one week to six weeks; during this period no significant change in visual field border was obtained (t test: $P > 0.30$).

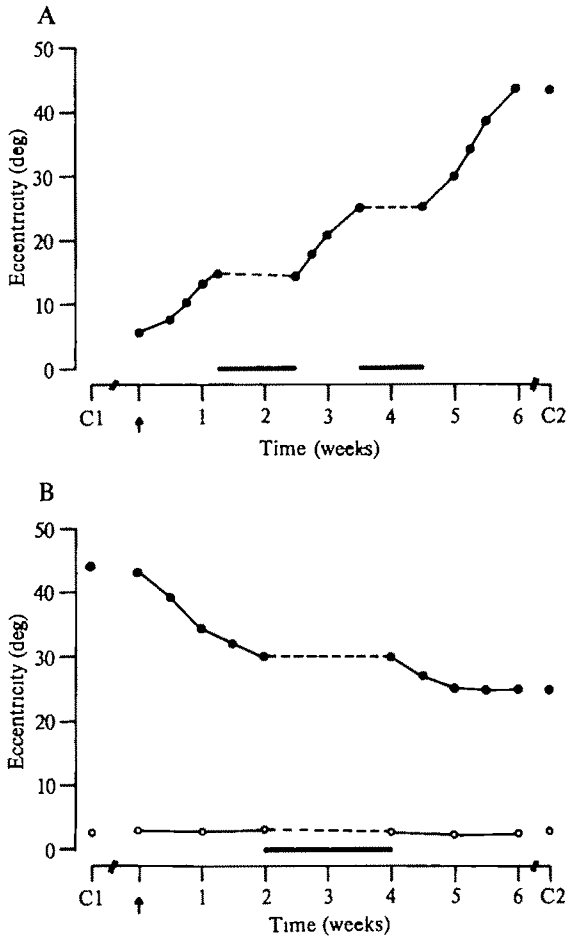

FIG. 5. Enlargement of binocular visual field (for patients' field plots, *see* figs. 2A and 3A) in periods with (continuous lines) and in intervals without systematic treatment (broken lines). C1 = control measurement A, three weeks after the occurrence of posterior cerebral infarction and B, two weeks after infarction. C2 = control perimetry six months after the end of treatment in A and B. Open circles in B indicate eccentricity of the inner border of the scotoma not showing any change even in periods with systematic treatment.

The increase in visual field size remained stable even after treatment had been completed. Perimetric measurements, after at least four months from the end of training in all 44 patients who benefited from treatment, as well as for the remaining 11 patients without any field increase, revealed no significant change in field size when compared with the results of perimetric testing immediately after the end of visual training (Wilcoxon test: $P > 0.15$).

Return of Visual Function other than Light Vision

Return of colour and form vision. In the recovered field region, colour and form recognition returned in most of the patients who had suffered posterior cerebral

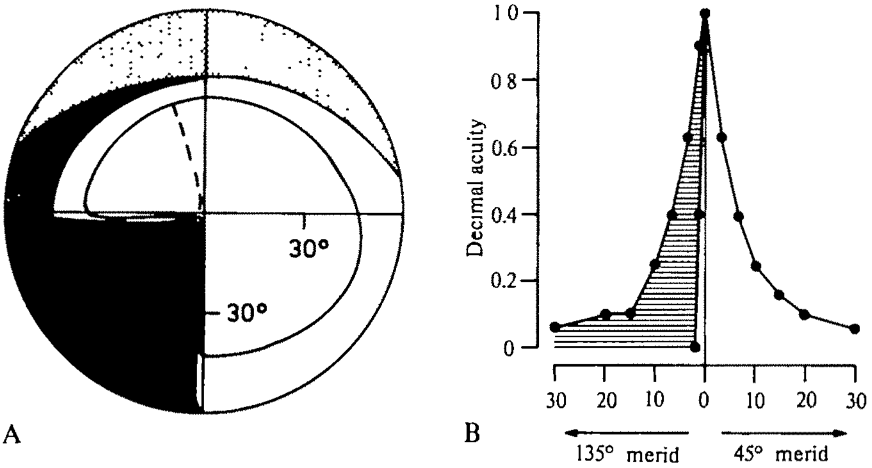

FIG. 6. Return of colour and form vision in the field region recovered from scotoma (for field plot, *see* fig. 2A). A, extent of binocular colour field before (broken line) and after (continuous line) recovery of visual field in the left upper quadrant. B, binocular visual acuity profile along the horizontal axis before and after recovery. The hatched area indicates the region of return of form acuity after treatment.

infarction; only in 2 out of 36 patients exhibiting recovery of visual field from scotoma (6%) was recovery limited to light perception. Fig. 6 shows a typical example for the return of light, colour and form vision in the field region recovered from scotoma (the same patient as in fig. 2A). In contrast, in 8 out of 9 patients with closed head trauma showing field enlargement after training, only light vision returned, as shown in fig. 7 for one patient. Even after field size increased from 2.5 deg to 42 deg eccentricity along the left horizontal axis (*see* fig. 7A), neither colour (fig. 7B) nor form vision reappeared in the recovered field region (fig. 7D). Again, light sensitivity remained reduced as compared to the corresponding eccentricities in the intact right hemifield (fig. 7C).

Detection and recognition of visual stimuli presented tachistoscopically in the recovered field region. Table 3 shows the results of detection of light targets presented simultaneously in the recovered field region and in the corresponding part of the intact hemifield, for 2 patients exhibiting a rather large increase in field size after treatment (Case 1, fig. 2A; Case 2, fig. 7A) and for 1 patient not showing any change in field size (Case 3, fig. 4A). Before training, none of the patients was aware of, or could report light targets presented in the scotomatous region. After recovery however, Cases 1 and 2 reported seeing, and detected correctly, the light targets appearing within the recovered region. In contrast, Case 3 was never aware of, and did not report, any light target presented beyond 5 deg eccentricity in the blind hemifield, either before or after visual training. In 'catch' trials (one target presented either in the left or right hemifield), patients never reported two, but always, correctly, one target.

Recognition performance, that is, the number of numerals reported correctly, before and after treatment, is shown in Table 4 for the same 3 patients (Cases 1-3)

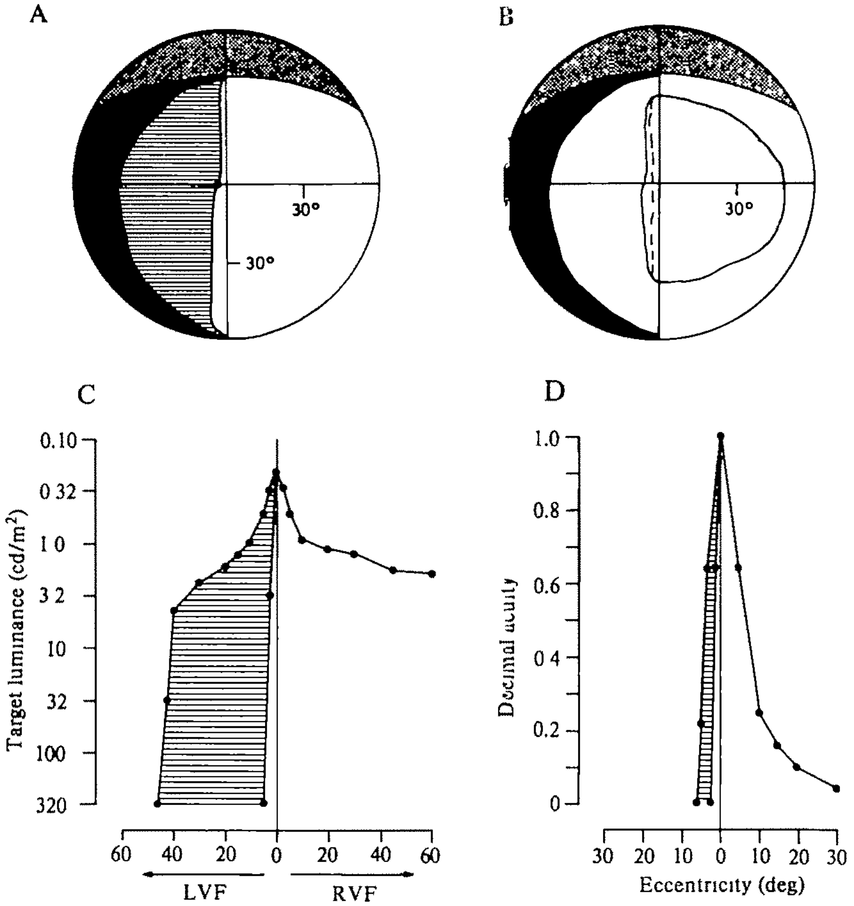

FIG. 7. Visual field enlargement (in A, hatched area), colour visual field (B) before (broken line) and after recovery (continuous line), light sensitivity profile (C, hatched area corresponds to that in A), and acuity profile along the horizontal axis (hatched area indicates return after recovery), in a 25-year-old patient who had suffered closed head trauma. D shows lack of recovery of form vision (cf. fig. 6B). Time since lesion = 22 weeks. Note cerebral hemiamblyopia in the recovered left hemifield, beyond 6 deg visual angle. LVF, RVF = left and right visual half-field.

presented in the last section. After training, all patients except Case 3 were able to recognize significantly more numerals, beginning at the vertical axis, than before enlargement of the visual field (χ^2-test: $P < 0.001$). Identification performance for Case 2 was somewhat lower than for Case 1 because form acuity had not returned fully after training (*see* fig. 7D).

Patients' Subjective Reports Before and After Treatment

Before treatment, all patients, except 2 showing a residual field of about 30 deg visual angle, reported awareness of their field defect. After treatment, patients' reports differed depending on the eccentricity of the field border. Patients with field loss reaching near to the fovea and an increase in field size in the perifoveal region,

TABLE 3. DETECTION PERFORMANCE*

Case 1. 135 deg meridian–45 deg meridian (IVF)

	10 deg	*40 deg*
Before training	00	00
After training	20	18

Case 2. 180 deg meridian–0 deg meridian (IVF)

	05 deg	*10 deg*
Before training	00	00
After training	20	19

Case 3. 0 deg meridian–180 deg meridian (IVF)

	06 deg	*10 deg*
Before training	00	00
After training	00	00

* No. of correct responses in 20 trials/condition of bilaterally simultaneous light targets presented at different eccentricities before and after training in 3 patients. (Case 3 did not show any field enlargement after treatment. *See* text.) IVF = intact visual field.

TABLE 4. RECOGNITION OF NUMERALS*

Case 1. IVF: right upper quadrant (5 deg above horizontal axis).
Affected side: left upper quadrant (same field region)

IVF 09	Affected field:	Before training	03
		After training	08

Case 2. IVF: right horizontal meridian.
Affected side: left horizontal meridian

IVF 09	Affected field:	Before training	01
		After training	08

Case 3. IVF: left horizontal axis.
Affected side: right horizontal axis

IVF 10	Affected field:	Before training	03
		After training	04

* No. of correctly recognized numerals out of 10 stimuli presented tachistoscopically for 80 ms, before and after training. IVF = intact visual field.

without exception reported an enlargement of their visual field. In contrast, patients with loss of more peripheral parts of the visual field (beyond about 10 deg eccentricity) reported only an enlargement when the increase exceeded about 10 deg visual angle. Thus a minimum amount of enlargement, depending, however, on eccentricity, seems essential before it is noticed by the patient. In contrast to the reports of patients who had benefited from treatment, none of the patients without field enlargement reported an increase in field size.

With regard to visual disabilities, before treatment patients complained most frequently of bumping against obstacles or people on the affected side and of difficulties with reading. Before treatment 71 per cent of the patients reported severe, and 25 per cent moderate difficulties with avoiding obstacles or persons. Two (4%) did not report any disability; both showed a residual visual field of more than 25 deg in the affected hemifield. After treatment, 51 per cent of patients no longer complained of these difficulties, while the remaining 49 per cent reported moderate (20%) or even severe problems (29%). Thus the percentage of patients complaining about difficulties in avoiding obstacles at the affected side dropped from 96 to 49 per cent after treatment.

Reading performance before and after treatment. Before training, patients with sparing of less than about 3 deg visual angle along the horizontal axis (32 or 58%) complained of severe difficulties with reading. They reported that they could no longer read because words appeared 'cut off' at their beginning or at their end. Patients with sparing of more than 3 deg visual angle (42%) did not report any reading disabilities. After treatment, 7 patients (13%) reported difficulties with reading, mainly in terms of being slow or, in cases with a left-sided field defect near the fovea, of omitting the first word(s). Sparing of visual field in these cases did not exceed 3 deg visual angle. Five hemianopic patients who had not benefited from treatment, all of them not showing more than 2 deg residual field, further complained about severe problems in reading. Thus, in total, 12 patients (22% as compared with 58% before treatment) remained with severe or moderate difficulties with reading after treatment.

In order to obtain quantitative evidence on the improvement in reading after training, as suggested by patients' reports, reading time and errors were also recorded before and after training using a standardized text. This text consisted of 40 lines and 9 words of different length (2 to 12 letters) in each line. Half of the text, that is 20 rows (180 words), was presented to the patients before, and the other half after training. The text was taken from the same author, and both versions were of about the same difficulty. The patients were asked to read aloud and to aim at errorless reading rather than reading fast. Results from 20 hemianopic patients (10 with left-sided, 10 with right-sided field loss) are presented, all of them showing a residual field not exceeding 2.5 deg visual angle before treatment. Half of the group showed, after treatment, an increase in field size exceeding 1.5 deg visual angle (group A), the other half did not (group B). The number of patients exhibiting a left- or right-sided hemianopia was identical in both groups (5 with left-, 5 with right-sided field loss). In addition, 10 normal subjects (aged 25 to 62 years) were tested for comparison. This group read both halves of the text correctly; mean reading time for the first part was 55 s (range 46 to 88 s), and for the second 57 s (range 42 to 96 s). Table 5 shows mean reading time and mean errors (uncorrected by the patient) and visual field border along the horizontal axis in the affected hemifield, before and after training, for both groups.

Before treatment both groups showed about the same impairment in reading with respect to reading time and reading errors; both parameters did not differ significantly between groups (t test: $P > 0.10$ for reading time and $P > 0.50$ for reading errors). The side of the field defect, however, affected reading performance in a characteristic way. Patients suffering from a left hemianopia showed significantly more reading errors than right-hemianopic patients (t test: $P < 0.01$ in group A; $P < 0.02$ in group B) because they more frequently omitted words, or parts of words, at the left end of the line. In contrast, patients with right hemianopia required significantly more time (t test: $P < 0.01$) because they returned repeatedly to the beginning of words consisting of more than five letters in order to comprehend them.

After treatment, both reading time and number of errors were significantly reduced in both groups as compared with reading performance before treatment (t test: lowest $P < 0.02$), even though both parameters remained significantly different from normal values (t test: $P < 0.01$). However, group A performed significantly better than group B, with respect to both reading time and reading

TABLE 5. READING PERFORMANCE*

		Mean	*Range*
A.	Field border before	1.5	0.5–2.5
	Field border after	3.4	2.0–5.0
	Reading time before	5.8	3.3–8.5
	Reading time after	2.6	1.2–4.5
	Reading errors before	14.7	08–29
	Reading errors after	03.5	02–07
B.	Field border before	1.7	1.0–2.5
	Field border after	2.3	1.5–3.0
	Reading time before	5.9	3.7–7.6
	Reading time after	4.8	3.0–6.3
	Reading errors before	12.8	09–31
	Reading errors after	07.3	03–16

* Expressed as mean reading time, in min, and mean reading errors, and mean eccentricity of visual field border (in deg visual angle along the horizontal axis) before and after treatment, in hemianopic patients (A) with and (B) without field enlargement (n = 10 per group).

errors (t test: $P < 0.01$). Furthermore, patients with a left or right hemianopia in group A no longer differed significantly with respect to reading time and reading errors (t test: $P > 0.20$), whereas in the second group the difference persisted (t test: $P < 0.01$ for reading time; $P < 0.02$ for reading errors).

To summarize, both groups showed a significant improvement in reading performance, but the group with an increased visual field after treatment performed significantly better than the other group with field enlargement. However, patients without field enlargement but an improved reading performance, as assessed quantitatively, did not report the same reduction of their reading disabilities as did patients with field enlargement. The main difficulty of which they complained was that they were not able to read fast enough to comprehend the text. In fact the mean decrease in reading time was only about 1 s, which is negligible as compared with 3.2 s in group A.

Controls

In a series of perimetric control measurements, using the Tübinger perimeter, we attempted to exclude various artefacts which could have been partly responsible for the observed visual field enlargement. These controls dealt with accuracy and reliability of perimetric measurements, casual or persistent shift of gaze towards the affected hemifield during perimetry, and the influence of response criteria on perimetric determination of the visual field border. Furthermore, we also treated one patient in the intact hemifield, using the same training procedure, after recovery of the affected hemifield, in order to determine the effect of treatment in a normal half-field.

Treatment in the normal hemifield did not result in any significant change in threshold for light detection. The patient (for field plot, *see* fig. 2A) participating in this test showed recovery of the left upper quadrants, on the affected side, after 900 trials. About the same amount of treatment (960 trials in 8 sessions) was performed along the 45 deg meridian in the intact right hemifield. We compared light difference thresholds, as determined by static perimetry, before and after training sessions, at 2.5, 5, 10, 20 and 30 deg eccentricity. Light difference thresholds did not differ significantly either within (t test: $P > 0.20$) or between sessions (t test: $P > 0.50$). The largest difference between threshold measurements was 0.15 log units. These observations indicate that the same treatment which led to an enlargement in the affected hemifield did not result in an improvement in light sensitivity in the intact half-field.

Accuracy and reliability of visual field mapping were tested by calculating the error of measurement and by comparing it with the degree of enlargement found after recovery. Perimetric testing was carried out twice, on two different days, by two independent perimetrists with 5 patients (4 with, 1 without recovery), before and after training. One perimetrist was not informed whether the patients were being treated or not. Binocular measurements were performed at random at selected positions along the field border. Target size was 116 min arc of visual angle. After

10 trials a break of about 1 min was introduced. Patients were not informed as to the measurement positions.

Data are presented for 2 patients whose field plots are shown above (Case 1, fig. 2A; Case 2, fig. 4A). The field positions where these measurements were undertaken are indicated by filled circles in the corresponding figures. Case 1 showed a considerable amount of enlargement after training, whereas Case 2 did not benefit from training (increase: 0.5 deg visual angle).

Table 6 shows the results of repeated perimetric testing for Cases 1 and 2. In these, as well as in the 3 other patients, the range of measurements was found to be below 1 deg visual angle for the inner part of the visual field (i.e. up to 15 deg eccentricity) and 1 to 2.5 deg visual angle for more peripheral field regions. Thus, the largest error of perimetric measurements was ± 0.5 deg visual angle in the inner field region and ± 1.75 deg beyond 15 deg eccentricity.

In field regions where no increase was found after visual training, perimetric measurements did not differ significantly before and after visual training (t test: $P > 0.20$, for all cases).

For all 5 patients tested by both perimetrists, a high correspondence of perimetric results between sessions and between perimetrists was found. In no condition (5 patients, 2 sessions, 2 perimetrists) was a significant difference found (t test: lowest $P > 0.20$), except for one repetition performed by the second perimetrist with one patient, where a mean difference of 15 min arc of visual angle was found to reach significance (t test: $0.01 < P < 0.02$).

Casual shifts of fixation during perimetry would be expected to result in an inconsistent fluctuation of the field border and, therefore, in a high variability of perimetric measurements. As shown above, the accuracy and reliability of perimetric measurements clearly contradicts this assumption. Any consistent shift of gaze towards the stimulus to be detected would result in a corresponding shift of the border of the visual field along the whole vertical axis (*see* Glaser, 1978, p. 158). However, comparing the field border along the vertical axis before and after treatment in 10 hemianopic patients benefiting from treatment (range of enlargement: 5 to 12 deg visual angle), we could not find any evidence for a significant shift of the vertical border of the hemianopia outside the region of recovery (t test: $P > 0.20$). Furthermore, as Teuber *et al.* (1960) have pointed out, any persistent shift of the field border towards the side of the field defect, due to eccentric fixation, is accompanied by a shift of the blind spot towards the scotomatous hemifield. We plotted the position of the blind spot in 12 patients (7 with a field increase, 5 without any field enlargement) before and after visual training. Target size was 27 min of arc visual angle, target luminance 320 cd/m^2. Using this stimulus condition, the optic disc could be plotted as an absolutely dense region. In no case did we find a significant change in the eccentricity of the position of the blind spot (t test: $P > 0.50$ for both groups; *see* Table 7) as an indication for a shift of gaze after visual training. The difference between the positions of the blind spot before and after training was in the range of 30 min of arc only. The same range was found in those patients who

TABLE 6. PERIMETRIC CONTROL MEASUREMENTS*

	Mean (deg)	*±SD*	*Range*
Case 1. 180 deg meridian			
Before training			
Perimetrist 1			
Session 1	2.18	0.25	01.75–02.50
Session 2	2.10	0.26	02.00–02.50
Perimetrist 2			
Session 1	2.13	0.28	01.75–02.50
Session 2	2.28	0.29	02.00–02.50
After training			
Perimetrist 1			
Session 1	35.35	0.53	34.50–37.00
Session 2	34.65	0.48	33.50–35.50
Perimetrist 2			
Session 1	34.10	0.39	32.50–35.50
Session 2	34.90	0·88	33·00–35.50
Case 2. 0 deg meridian			
Before training			
Perimetrist 1			
Session 1	02.03	0.14	01.75–02.25
Session 2	01.95	0.20	01.75–02.25
Perimetrist 2			
Session 1	02.03	0.18	01.75–02.25
Session 2	02.18	0.24	01.75–02.50
After training			
Perimetrist 1			
Session 1	02.93	0.24	02.50–03.25
Session 2	03.03	0.18	02.75–03.25
Perimetrist 2			
Session 1	03.05	0.16	02.75–03.25
Session 2	03.30	0.20	03.00–03.50

* In 2 patients (for visual field plots, *see* figs. 2A and 4A) before and after visual training, performed by 2 perimetrists in 2 different sessions (n = 20/condition).

did not benefit from visual training, indicating that the optic disc could be plotted reliably.

Finally, the question remains as to whether the increase in field size observed after visual training may be based on a change in response criterion rather than from recovery. Data are presented from 2 patients (Case 1, field plot, *see* fig. 2A; Case 2, field plot, *see* fig. 4A). Before treatment, both patients exhibited about the same amount of residual field along the horizontal meridian in the affected hemifield

TABLE 7. POSITION OF BLIND SPOT*

A. Patients with field enlargement

Case	*Enlargement (deg)*	*Position before (deg)*	*After (deg)*
1	02	14.0	13.5
2	07	14.5	14.0
3	09	13.5	13.5
4	10	13.5	14.0
5	15	14.0	14.5
6	28	14.5	14.0
7	38	13.5	13.5

B. Patients without field enlargement (< 1.5 deg)

Case	*Enlargement (deg)*	*Position before (deg)*	*After (deg)*
1	0.0	13.5	13.5
2	0.5	13.5	14.0
3	0.5	14.0	13.5
4	1.0	14.5	14.5
5	1.0	14.0	14.5

* Inner side from the point of fixation in the intact hemifield, in deg visual angle, before and after visual training in (A) a group of patients exhibiting field enlargement and (B) in a group without enlargement.

(2.5 deg visual angle). After treatment, Case 1 showed an increase of 36 deg after training along the left horizontal axis, but no enlargement in the lower quadrants. In contrast, Case 2 did not show any significant field increase.

Both patients were tested under binocular viewing conditions at the field border, and within the scotomatous region, using two criteria ('seeing light', and 'guessing light'). Two different 'guessing'-conditions were used, namely with and without bias. In the former condition, the patients were told that the light target would appear more often than the 'blank'. The number of presentations, however, remained the same.

The measurements were carried out with the Tübinger perimeter. Target size was again 116 min arc of visual angle in all conditions. Targets were presented for 500 ms at the field border or 2 deg away in the scotomatous region. The patients were instructed to fixate the red spot in the centre of the sphere and to press the buzzer key either when they could see light, or 'guessed' that light had been presented. In each condition, 100 trials were performed; half of them were test trials (light spot on), the other half 'blanks' (no light target presented). The order of presentation was random, and the patients were not informed as to the order of presentation or their performance. After every 20 trials a break of 1 min was introduced.

Tables 8 and 9 show the outcome of these tests for both patients. The patients had no difficulty in detecting the presence of the target almost correctly when presented at the field border, where they could see the target. They were never able to do so for targets presented 2 deg away from the field border and did not report any awareness of light. Even when they were 'biased' to expect the target more often and thus to have to press the buzzer key more frequently, their correct responses did not differ significantly from the number of incorrect responses (χ^2-test: $P > 0.30$ for both

TABLE 8 EFFECT OF CHANGE IN RESPONSE CRITERION ON ECCENTRICITY OF VISUAL FIELD BORDER*

	Response	*No response*
A. Before treatment		
(a) Visual field border, 2.5 deg eccentricity		
Light targets	46 (92)	04 (08)
'Blanks'	02 (04)	48 (96)
(b) 4.5 deg eccentricity		
(i) Light targets	10 (20)	40 (80)
'Blanks'	08 (16)	42 (84)
(ii) Light targets	26 (52)	24 (48)
'Blanks'	24 (48)	26 (52)
(c) Left lower quadrant		
(i) Light targets	12 (24)	38 (76)
'Blanks'	10 (20)	40 (80)
(ii) Light targets	17 (34)	33 (66)
'Blanks'	19 (38)	31 (62)
B. After treatment		
(a) Visual field border, 36 deg eccentricity		
Light targets	47 (94)	03 (06)
'Blanks'	02 (04)	48 (96)
(b) 38 deg eccentricity		
(i) Light targets	10 (20)	40 (80)
'Blanks'	12 (24)	38 (76)
(ii) Light targets	16 (32)	34 (68)
'Blanks'	14 (28)	36 (72)
(c) Left lower quadrant		
(i) Light targets	11 (22)	39 (78)
'Blanks'	13 (26)	37 (74)
(ii) Light targets	16 (32)	34 (68)
'Blanks'	17 (34)	33 (66)

* Effect of criterion change ('guessing' instead of 'seeing' light) before and after treatment in a patient with field enlargement (Case 1; for field plot, *see* fig. 2A). Targets were presented either at the field border for light vision (a) or 2.0 deg beyond this border (b, c). Eccentricity values refer to the left horizontal meridian in (a) and (b), and to the vertical axis in the left lower quadrant in (c) (*see* black dots in fig. 2A). No. of responses to light targets (percentage in brackets) and to 'blanks' (50 trials per condition). (i) responses without any bias; (ii) responses with bias.

patients in both conditions). Thus the two response criteria did not lead to different perimetric results in either patient before (t test: $P > 0.50$) or after treatment (t test: $P > 0.50$).

DISCUSSION

Spontaneous Recovery and Recovery after Treatment

Spontaneous recovery was negligible in our patients; other authors, in contrast, have reported a higher percentage of patients showing spontaneous recovery, but did not specify this in terms of quantitative perimetric results (Gloning *et al.*, 1968; Teuber, 1975; Hier *et al.*, 1983). Furthermore, systematic follow-up was not performed in these studies, so that no firm conclusion can be drawn as to the time course of spontaneous recovery from visual field defects. The visual field changes reported by these authors therefore cannot be compared directly with our perimetric data.

The majority of patients benefited from treatment, showing an enlargement ranging from 1.5 to 38 deg visual angle. In most of the patients who had suffered

TABLE 9. EFFECT OF CHANGE IN RESPONSE CRITERION ON ECCENTRICITY OF VISUAL FIELD BORDER*

	Response	*No response*
A. Before treatment		
(a) Visual field border (2.5 deg eccentricity)		
Light targets	42 (84)	08 (16)
'Blanks'	02 (04)	48 (96)
(b) 4.5 deg eccentricity		
(i) Light targets	02 (04)	48 (96)
'Blanks'	04 (08)	46 (92)
(ii) Light targets	14 (28)	36 (72)
'Blanks'	16 (32)	34 (68)
B. After treatment		
(a) Visual field border (3 deg eccentricity)		
Light targets	47 (94)	03 (06)
'Blanks'	03 (06)	47 (94)
(b) 5.0 deg eccentricity		
(i) Light targets	04 (08)	46 (92)
'Blanks'	03 (06)	47 (94)
(ii) Light targets	18 (36)	32 (64)
'Blanks'	16 (32)	34 (68)

* Effect of change in a patient without field enlargement (Case 2; for field plot, *see* fig. 4A). Targets were presented before and after treatment at the field border for light vision ((a) right horizontal meridian) and 2.0 deg beyond (b). Further details as in Table 8.

posterior cerebral artery infarction, colour and form vision also returned in the recovered field region. In contrast, colour and form vision did not return in most of the patients who had suffered closed head trauma. It therefore seems that damage to the postgeniculate visual pathway from closed head trauma typically results in cerebral hemiamblyopia, as has also been reported for patients suffering from homonymous field loss after gunshot injuries (*see* Poppelreuter, 1917; Hine, 1918; Wilson, 1919; Teuber *et al.*, 1960).

The enlargement of the visual field can hardly be attributed to spontaneous recovery, since in periods without systematic treatment no significant increase in field size was observed. It can be concluded, therefore, that systematic treatment was the crucial variable for recovery. The enlarged field region remained unchanged even after the treatment had ended. Thus recovery of visual field may be considered as a long-term effect.

Variables not Affecting Field Enlargement

Visual field recovery did not depend either on patients or on damage variables. In relation to the aetiology of the damage (i.e. posterior cerebral infarction or closed head trauma), no firm conclusion can be drawn because of the small number of patients with closed head trauma in our group. It is interesting to note that the time interval after brain damage did not influence field enlargement by systematic treatment, as has been stated for spontaneous recovery (*see* Teuber, 1975). Even the amount of training required was not significantly correlated with the time from the occurrence of the lesion.

An important and critical issue is the question as to what extent the observed field enlargement could be attributed to unstable or eccentric fixation, or to a change in detection criterion, which would result in an artefactual change in the borders of the field. The outcome of the control experiments, however, does not support any interpretation of the field enlargement as being a consequence of such artefacts.

According to the accuracy and reliability of our perimetric measurements, it seemed justifiable to accept an increase of at least 1.5 deg visual angle as a treatment effect, since this value is well outside the range of measurement variability. This limit is conservative in relation to the possible influence of unstable fixation from eye drift or microsaccades (amounting, at the most, to 50 min of arc; *see* Alpern, 1972; Gerrits *et al.*, 1984), as well as the variability of perimetric measurements.

The accuracy and reliability of perimetric measurements, as obtained in our study, are in close agreement with that reported by other authors. Teuber *et al.* (1960), in their study of 46 patients exhibiting visual field defects after penetrating missile wounds of the brain, found variations in the fields between assessments of ± 1 deg within 5 deg visual angle in the central visual field, and within ± 2.5 deg for the peripheral regions. Williams and Gassel (1962) reported an accuracy in mapping the field border of the order of 1 deg in their 35 patients with brain damage from various causes. In patients with marked fixation irregularity, the accuracy varied from this range up to approximately 3 deg.

These arguments make it highly unlikely that field enlargement was caused by a persistent shift of gaze, either due to head deviation, eccentric fixation or eye movement strategies, developed during treatment and used only during perimetry, thus simulating recovery, as was proposed by Bach-y-Rita (1983).

Finally, it may be questioned whether the field border could correctly be determined by 'conventional' perimetric testing using a criterion based on 'seeing light'. Obviously any visual capacity not leading to conscious light vision would remain undetected by perimetric testing based on any criterion of 'seeing light'. However, the data presented, using different response criteria, demonstrate that the border of the visual field can be estimated accurately and reliably using a criterion based on 'seeing light'. Guessing the presence of the light target presented 2 deg away from the 'conventional' field border did not reveal any 'subthreshold' light sensitivity which was not detected by the usual perimetric testing, and which could produce an expansion of the visual field if patients, after treatment, might have changed their response criterion from 'seeing light' to 'guessing light'.

The enlargement of visual field cannot be accounted for in terms of attentional effects, which have been reported to improve visual efficiency of target detection at the cued location in the visual field (*see* Posner *et al.*, 1982). If orientation of attention were the only critical variable, recovery of vision would be expected in all field regions subjected to training. As demonstrated here, vision did not recover in all parts of the field, despite the same training being applied. Furthermore, patients who did not benefit from treatment showed an improved light sensitivity in the transition zone between the intact field and the scotomatous region, but this improvement did not lead to a change in the border of the visual field (*see*, for example, fig. 4).

In an earlier study (Zihl and von Cramon, 1979*b*) we found that threshold level for light detection in the affected hemifield can be influenced by cueing, especially at the visual field border. However, even this orientation of attention did not result in visual field enlargement.

It must be emphasized that the visual field enlargement, as found in our patients after treatment, must not be confused with visual capacities obtained in regions of the field that are perimetrically blind (Campion *et al.*, 1983), and labelled as 'blindsight'. Patients showing visual field enlargement possessed *conscious* vision for all stimuli appearing within this region; not only were they able to detect and recognize visual stimuli but could also name them correctly. Furthermore, the patients reported the same quality of vision for colours, forms and letters presented within their recovered field region as well as for objects or scenes in a natural environment. Patients exhibiting cerebral amblyopia in the recovered field region were, of course, not able to recognize colours or forms presented within this region but were always aware of, and could report the presence of the stimuli. The quality of vision in the recovered field regions therefore differs clearly from that reported in patients possessing the ability to 'guess' the appearance and position of a light spot or crude pattern (for a review concerning 'blindsight', *see* Weiskrantz, 1978). It should be added here that, as shown earlier (Zihl, 1980, 1981), visual field recovery is not linked to the patient's ability to locate unseen targets in the perimetrically blind hemifield. Localization performance in a previously blind field region was not found to be correlated with the degree of recovery.

Patients' Report on their Visual Disabilities and their Alleviation after Treatment

Visual field enlargement was not reported by all patients who had benefited from training. It seems that field enlargement in the central region (between 1 and 5 deg) can be noticed best by the patient probably because of its influence on reading performance and on simultaneous perception of objects, faces and scenes, that is, without large eye movements or head turning. In relation to field enlargement in the periphery, only patients with a restricted peripheral field before training and an increase of at least 10 deg reported this enlargement. Patients' reports must therefore be accepted somewhat cautiously as to self-evaluation of the extent of field loss and the effect of treatment and cannot be used without quantitative perimetric testing (*see also* Critchley, 1949; Gassel and Williams, 1963*b*). On the other hand, no patient not benefiting from treatment in terms of field enlargement reported an enlargement after treatment.

The reports from patients as to their reading performance were in close agreement with results based on quantitative testing, both before and after treatment. Quantitatively assessed improvement in reading performance, however, cannot be taken as evidence for an increase in field size, since patients without field enlargement also showed a significantly improved performance. Improvement in reading performance cannot be related, therefore, to field enlargement only, but may also be attributed to an improved strategy, for example, in actively searching the text required for reading. It has been shown that hemianopic patients may develop eye or head-movement strategies in order to compensate for their field loss (*see* Gassell and Williams, 1963*a*; Meienberg *et al.*, 1981; Zangemeister *et al.*, 1982). It is interesting to note, however, that patients with an improved reading performance, but without an increase in field size, were not able to evaluate their reading performance as being distinctly better after training. In contrast, all patients showing an improvement in reading and an enlargement of the perifoveal field unequivocally evaluated their reading performance as improved.

Possible Neural Mechanism(s) Underlying Visual Field Recovery from Scotoma

The neural mechanisms underlying the observed visual field recovery from scotoma after treatment in patients with postgeniculate damage are not yet clear. However, taking into consideration arguments from studies both in man and primates, hypotheses can be generated about the site of recovery and the underlying neural mechanism(s). Obviously these hypotheses must remain speculative since they lack direct support. Before presenting these arguments, it may be of help to discuss some of the prerequisites essential for postgeniculate visual functioning.

Visual information must be transmitted *via* the optic radiation to the primary termination site, the first visual area (or Brodmann's area 17). This area contains a topographically arranged representation of the retinal surface, and serves in some way to distribute the various dimensions of the input among the various visual areas beyond the striate cortex that are responsible for the analysis of these stimulus dimensions, such as colour, orientation and movement (*see* Zeki, 1978). Damage to the optic radiation results either in a homonymous visual field loss or in cerebral hemiamblyopia (*see* Polyak, 1957). Damage to area 17 leads to homonymous field loss and, additionally, to the abolition of transmission of visual information to the (topographically) corresponding regions in the prestriate cortex. Finally, damage to parts of the prestriate cortex results in (selective) loss of visual functions, such as colour or movement vision (*see*, for example, Samelsohn, 1881; Zihl *et al.*, 1983), leaving the visual field for light vision intact.

We suggest that recovery probably occurs at the striate cortex level for the following reasons. Damage to the striate cortex would result in a corresponding homonymous field defect for all visual abilities dependent on cortical mechanisms, since further visual cortical areas are no longer supplied with information about visual events stimulating the corresponding retinal region. Improvement in the functional efficiency of a part of the striate cortex that is not irreversibly damaged can lead to a corresponding recovery in the visual field from scotoma. Information can now again be transmitted to further visual areas, enabling the visual system to analyse various components of the visual environment as the basis for the perception of colour, form and movement, for example. This explains why patients are able to recognize colours and forms in the recovered field region.

Another argument favouring the striate cortex as the site for recovery from scotoma is the limitation of the treatment effect to a particular field region. It seems implausible that extrastriate visual areas of the visual cortex, not affected by the lesion, could substitute visual functioning for only a limited part of the visual field, while the other parts remain blind. Instead, it would be expected that these areas, in accordance with their coarser topography, would take over visual functioning for field regions much larger than those that recovered in most of our patients.

It remains to discuss how recovery can take place in the striate cortex, and which factors may underly such recovery. The field defect as initially plotted may result both from irreversible and reversible structural damage. Any visual field defect which does not recover spontaneously or cannot be reduced after treatment, has to be attributed to irreversible damage. Spontaneous visual field recovery from scotoma may be interpreted as the disappearance or reduction of the effect of reversible damage. The decrease in the size of the scotomatous region, after treatment, may also be interpreted as a reduction of the functional consequences of reversible damage, but exclusively depending on the systematic use of light stimuli, presented within the scotomatous region. Systematic saccadic activity alone, without presentation of a light target to be located, did not result in visual field enlargement (Zihl, 1981), neither did the visual stimulation of everyday life. Apparently depressed cortical function, due to reversible damage, cannot be compared with 'subthreshold' sensitivity. Even the use of signal detection methods did not reveal any sensitivity beyond visual field border, as determined by perimetric testing.

The morphological prerequisites for visual field enlargement, after treatment, in patients with postgeniculate damage remain unclear. As would be expected, an increase in visual field size obviously does not occur following a rather complete destruction of neuronal tissue in the relevant area. In patients with pseudocystic necrosis, showing hypodense lesions with values of less than 15 Hounsfield units

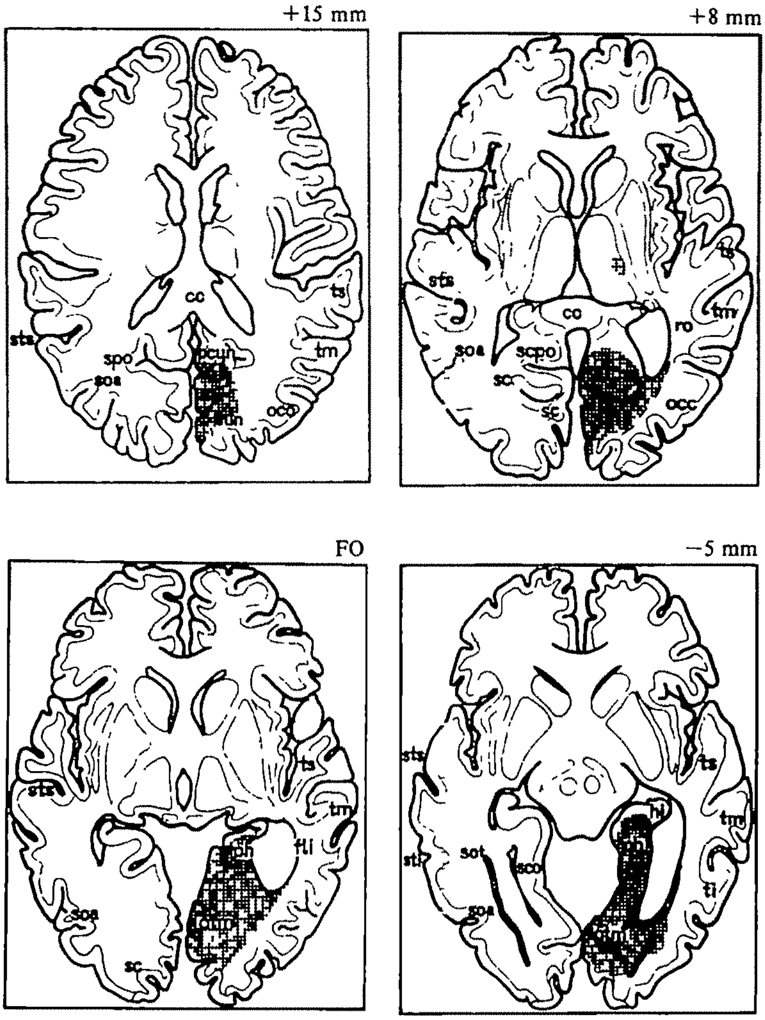

FIG. 8. Pseudocystic cerebral posterior infarction in a 58-year-old male patient, following proximal occlusion of the right posterior cerebral artery, with dilatation of the posterior and inferior horn of the lateral ventricle. CT scans seven weeks after infarction. The dark grey infarction area corresponds to density values < 15 HU. FO = fronto-occipital line. For further details *see* text.

(HU) in the CT scan, following, for example, posterior cerebral infarction, no treatment effect could be obtained. Fig. 8 gives an example of a patient with a presumably pseudocystic necrosis in the territory of the left posterior cerebral artery, with density values of less than 12 HU. Training was performed seven weeks after occurrence of brain infarction. Even after 980 trials, no visual field enlargement greater than 1.5 deg could be observed.

On the other hand, almost complete hemianopia was also present in patients with hypodense lesions with CT density values ranging between 20 and 30 HU. It should be emphasized that the visual field defects in these patients remained unchanged over a long period of time before training (up to 28 months). After systematic treatment, however, visual field enlargement was obtained in these patients, ranging from 1.5 to about 40 deg visual angle. In contrast, fig. 9 shows a patient with a right hemianopia following left posterior cerebral infarction. The hypodensity values are above 20 HU. Treatment was undertaken in this patient 13 weeks after the occurrence of infarction. Field enlargement, after 960 trials, was 25 deg visual angle.

It therefore seems reasonable to account for the treatment effect by assuming that neuronal damage was incomplete, so that residual neurons, which can subserve visual functioning, remained intact (*see* Lashley, 1938), provided that the optic radiation and further visual cortical areas were not (critically) damaged. With regard to the optic radiation, it has long been established (*see* Polyak, 1957) that lesions mainly affecting the optic radiation lead to cerebral hemiamblyopia. In relation to our observations on cerebral amblyopia (*see* p. 344), we may assume that in some patients who had suffered closed head trauma, cerebral hemiamblyopia may be due to white matter damage, so far undetectable in CT scans, apparently involving the optic radiation. This suggestion is supported by the observation that both patients showing hemiamblyopia after posterior cerebral artery infarction suffered from additional damage to the optic radiation.

ABBREVIATIONS

Abbreviations in figs. 8 and 9, referring only to the posterior parts of the brain (left hemisphere: sulci; right hemisphere: gyri)

sts = Superior temporal sulcus
spo = Parieto-occipital sulcus
soa = Anterior occipital sulcus
scpo = Calcarine parieto-occipital sulcus (common stem)
sc = Calcarine sulcus
sot = Occipitotemporal sulcus
sti = Inferior temporal sulcus
sco = Collateral sulcus
ts = Superior temporal gyrus
tm = Medial temporal gyrus
ti = Inferior temporal gyrus
occ = Occipital gyri
ph = Parahippocampal gyrus
otm = Medial occipitotemporal gyrus
otl = Lateral occipitotemporal gyrus
pcun = Precuneus
cun = Cuneus
hi = Hippocampus
un = Uncus hippocampi
na = Amygdala
fli = Inferior longitudinal fascicle
cc = Corpus callosum
ro = Optic radiation

The results reported in man can be compared with observations in monkeys after circumscribed striate cortex lesions (Cowey and Weiskrantz, 1963; Mohler and Wurtz, 1977). The return of detection and localization of visual stimuli after systematic treatment in these monkeys has been interpreted either in terms of spared visual cortical function or as dependent on extrastriate subcortical structures. However, neither electrophysiological data nor behavioural observations after striate cortex damage in monkeys would support the view that recovery of visual

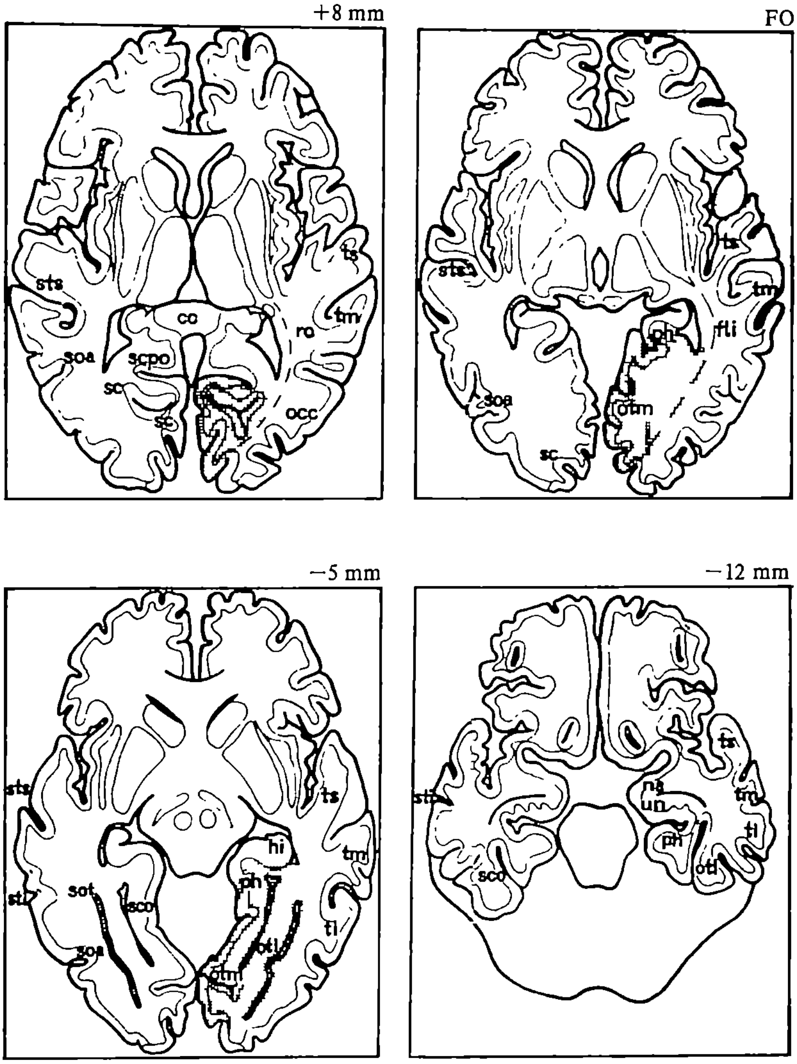

FIG. 9. Low-flow posterior cerebral infarction in a 29-year-old patient; CT scans thirteen weeks after infarction. The light grey infarction area corresponds to density values > 15 HU. FO = fronto-occipital line. For further details, *see* text.

field from scotoma, in our patients, is due to substitution of cortical function by subcortical structures, even though recovery may be mediated by them (Mohler and Wurtz, 1977). In this mediation of recovery, ascending reticular and/or catecholamine projections may play an essential role (*see* Singer, 1979).

To summarize, it can be concluded that enlargement of the visual field in patients with postgeniculate damage is possible, provided that the field defect does not result from completely irreversible brain damage. Functional efficiency, diminished by reversible damage, can be improved by systematic treatment. The treatment of homonymous field defects by the methods described can lead to an enlargement of the visual field, leading to a reduction of visual disability in the patients' everyday lives. This improvement, especially in patients with complete or nearly complete hemianopia, is an important prerequisite for rehabilitation (Savir *et al.*, 1977).

ACKNOWLEDGEMENTS

This work was supported in part by Deutsche Forschungsgemeinschaft. We are indebted to Christel Schmid for preparing the drawings, N. Mai and G. Müller for their help with the statistical evaluation of the data, and M. Elton and Ph. Hoole for grammatical corrections.

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(*Received April 13, 1984. Revised September 25, 1984. Accepted October 4, 1984*)

Brain (1985), **108**, 367–385

ALEXANDER'S DISEASE

A DISEASE OF ASTROCYTES

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SUMMARY

Alexander's disease is a rare and poorly understood cause of progressive neurological deterioration. Although the clinical history depends on the age group involved, the histological character and distribution of lesions tend to be uniform. The pathological features argue strongly that Alexander's disease represents a nonneoplastic disease of astrocytes. Numerous questions remain unanswered, including the factors responsible for the severity of the illness in the infantile group and the mechanism of demyelination secondary to astrocytic dysfunction. This series of 6 patients with Alexander's disease represents a wide spectrum of ages, enabling the pathological and clinical abnormalities to be related to a postulated mechanism of astrocytic dysfunction.

INTRODUCTION

The association of diffuse Rosenthal fibre formation with progressive neurological deterioration was first described by Alexander (1949) in an infant with megalencephaly. Since then, the pathological picture has been reiterated in various age groups with diverse symptomatology. Understanding of the illness has been hampered by its infrequent occurrence. In this report, the clinical features and pathological findings of 6 patients with Alexander's disease seen at The Hospital for Sick Children, Toronto, and the Toronto General Hospital are reviewed and the pathogenetic implications discussed.

CASE HISTORIES

Case 1

S.H. developed normally until the age of 6½ years when her school performance began to deteriorate. She was admitted to hospital when aged 7 years with a short history of headache and vomiting. Neurological examination was normal apart from the presence of mild weakness of the left lateral rectus muscle. The electroencephalogram (EEG) was diffusely abnormal showing excess theta and delta activity and a ventriculogram showed small ventricles. The ventricular pressure was reported as high, although the exact value was not recorded. A diagnosis of otitic hydrocephalus was made; she was treated with repeated lumbar punctures and her symptoms resolved.

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The child was again well until 7½ years of age at which time she had her first grand mal seizure. From this time, progressive deterioration in cognitive and motor function occurred. She gradually adopted a posture of generalized flexion associated with bradykinesia and rigidity. The physical abnormalities progressed and, in the latter part of her life, she was demented and bedridden. Seizures persisted throughout the course of her illness and she died of an intercurrent infection at the age of 15 years.

The brain in the fresh state weighed 1325 g. The gyral and sulcal pattern was normal as were coronal sections of the cerebral hemispheres. Transverse sections of the brainstem showed mild grey discolouration in the region of the dentate nucleus and softening around the substantia nigra.

Rosenthal fibres were prominently present in the subpial, periventricular and perivascular regions of the hemispheres. Scattered fibres were also seen elsewhere in the white matter and cortex. The basal nuclei had conspicuously more of these fibres than the surrounding white matter. In the periventricular region the involvement of grey and white matter was maximal and decreased with increasing distance from the ventricular surface; the degree of demyelination (used throughout this paper to mean loss of myelinated fibres) was commensurate with the extent of Rosenthal fibre formation.

In the midbrain, the aqueduct was distorted with ependymal disruption but it was patent. Rosenthal fibre formation was maximal in the tegmentum below the aqueduct. The cerebral peduncles were relatively spared with few fibres and good myelination. The dorsal tegmentum was the site of maximal involvement in the pons. The nuclear groups were severely involved in the basis pontis, whereas Rosenthal fibre formation and demyelination were minimal in the white matter. The medulla was more extensively affected than the rostral brainstem with the dorsal tegmentum showing the most severe involvement. Atypical astrocytes with vesicular nuclei and refractile intracytoplasmic inclusions were evident throughout the medulla. The pyramids were infiltrated with Rosenthal fibres and extensively demyelinated.

In the cerebellum, no Rosenthal fibres were present in the molecular, Purkinje or granular layers. The periventricular white matter was most severely affected and involvement diminished with distance from the ependymal surface. In the white matter superficial to the dentate nucleus, focal demyelination associated with perivascular mononuclear cell infiltration was present.

In all areas of the neuraxis, the neurons were well preserved regardless of the degree of Rosenthal fibre formation. However, axonal loss was seen in association with severe demyelination. Reactive astrocytes were present in all regions involved, although the degree of gliosis was mild.

Case 2

L.C. developed normally apart from a delay in walking (18 months). At the age of 3 years, periodic bouts of vomiting occurred and resolved spontaneously.

The patient was admitted to hospital at 5½ years of age for investigation of a clumsy gait, which had been present since she started walking. At that time, she was dysarthric with mildly spastic limbs, her IQ was 57 and an EEG was normal. The head was not enlarged. During the ensuing two years, her gait and speech deteriorated so that all attempts at walking were abandoned at 7 years of age. Generalized seizures occurred and intermittent projectile vomiting was present.

Deterioration continued until 14 years of age at which time she developed dysphagia, persistent vomiting and respiratory difficulty with inability to cough. Examination at this time showed a grossly retarded girl with little response to any stimuli. The cranial nerves including the gag reflex were intact. She had a flaccid quadriparesis with bilateral ankle clonus and flexor plantar responses. The tendon reflexes were present but sluggish. An EEG was grossly abnormal and showed diffuse slow wave activity. Her respirations became increasingly laboured and erratic and death occurred at 14 years of age.

The brain in the fresh state weighed 1255 g. Mild cortical atrophy and softening were present in the frontal area. The external surface of the cerebellum and brainstem were unremarkable. On coronal section, the lateral ventricles were mildly enlarged. The white matter throughout the hemispheres was spongy and compressed, with involvement maximal in the frontal lobes. In the cerebellum, there was pale discolouration of the dentate nucleus. Coronal sections of the brainstem and spinal cord were unremarkable.

In the cerebral hemispheres, striking subpial and subependymal Rosenthal fibre formation was seen. The fibres were also numerous in perivascular areas and individually in the neuropil. The deep white matter was more extensively involved than the superficial white matter or cortex. Demyelination was proportional to the degree of fibre formation. In the basal ganglia, the nuclear groups were less affected than the internal and external capsules.

Severe involvement was seen in the tegmentum, tectum and subpial region of the midbrain. The cerebral peduncles had significant Rosenthal fibre formation and showed moderate demyelination. The medulla was more severely involved than the rostral brainstem with striking subpial and perivascular aggregates. Maximal fibre formation was seen in the tegmentum below the fourth ventricle and around the inferior olivary nuclei. The pyramids were also extensively infiltrated and demyelinated. The optic nerves showed Rosenthal fibre formation in the body of the nerve and subpial region associated with patchy demyelination. Sections of the pons and cerebellum were not available for examination.

Neurons were well preserved throughout the neuraxis. Mild to moderate gliosis was seen in areas involved with Rosenthal fibre formation.

Case 3

B.D. developed normally until 14 months of age when he suffered his first grand mal seizure. At 17 months of age head circumference was 50.5 cm (98th centile) and he was functioning at the 8 to 10 month developmental level. Apart from generalized hypotonia no abnormality was present on physical examination.

Slight improvement occurred in neurological status until 2 years of age when the child was able to sit up, walked if held and showed improved muscle tone. Marked deterioration occurred after this. At the age of 2¾ years, head circumference was 56.3 cm (> 98th centile), he was grossly retarded with generalized hypotonia, hyperreflexia and bilateral extensor plantar responses. Pneumoencephalography showed mild ventricular enlargement. A brain biopsy was performed at this time. The patient died at 4 years of age of intercurrent infection after progressive neurological deterioration.

The right frontal surgical biopsy measured 1 × 0.5 × 0.5 cm and contained grey and white matter. No gross abnormalities were present. Rosenthal fibre deposition occurred maximally in the subpial and perivascular regions but was also scattered throughout the cortex and white matter. Reactive astrocytes were seen in the grey and white matter, particularly in the latter. Demyelination was moderate and was accompanied by axonal loss. No increase in cellularity was evident and neurons were preserved.

At autopsy the brain in the fresh state weighed 1720 g (normal = 1190 g). An arachnoid cyst occupied part of the vermis and separated the cerebellar hemispheres. The cerebral hemispheres were symmetrical and the gyri were large in conformity with the large size of the brain. No herniations were present. The brainstem and spinal cord were normal on external inspection. Coronal sections 1 cm thick of the cerebral hemispheres revealed that the white matter was soft and slightly cavitated and the thalamus and caudate were small compared with the size of the hemispheres (fig. 1). No other abnormalities were seen in the hemispheres or in coronal sections of the brainstem, cerebellum or spinal cord.

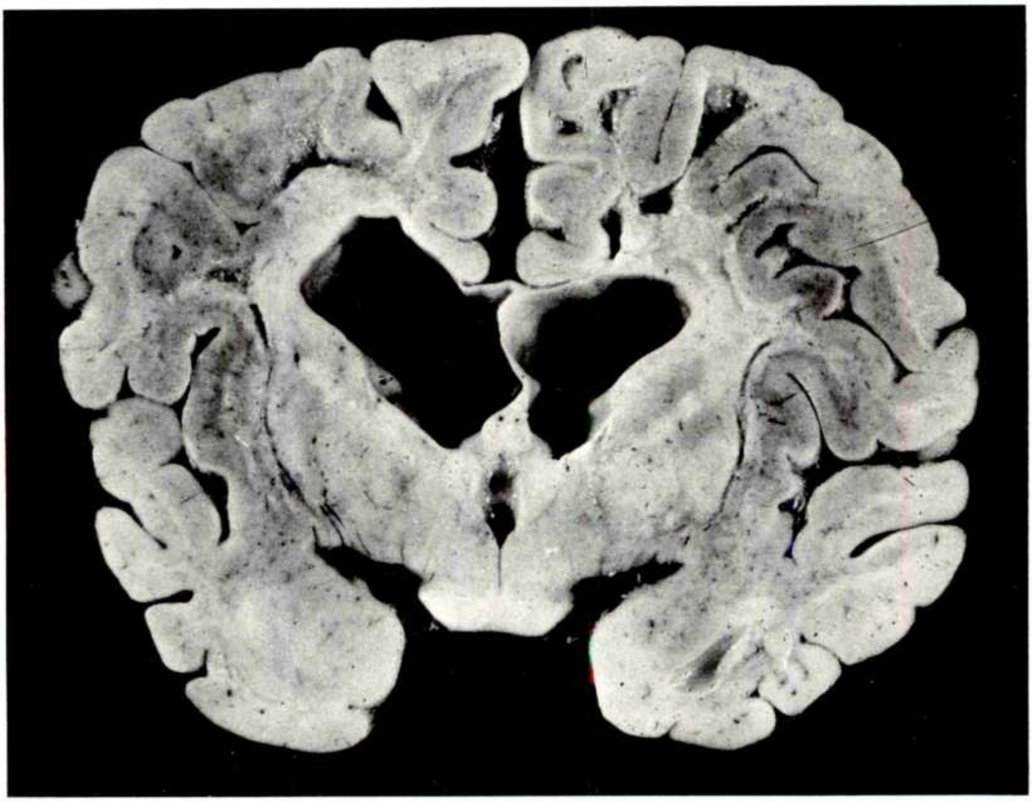

FIG. 1. Coronal section showing areas of demyelination with early subcortical cavitation. The ventricles are dilated.

In the hemispheres, Rosenthal fibre accumulation was seen in the subpial (fig. 2A), perivascular (fig. 2B) and subependymal regions. The white matter was more extensively involved than the cortex and Rosenthal fibre formation and demyelination in the white matter were most prominent in the deep hemispheres. In some areas the involvement extended to the corticomedullary junction without preservation of the arcuate fibres. The caudate and internal capsule were severely affected rostrally, whereas involvement diminished caudally. Myelin was well preserved at the genu of the internal capsule with little Rosenthal fibre formation.

In the thalamus, the grey matter was more extensively infiltrated than the white matter. Perivascular and subpial Rosenthal deposition was prominent in the brainstem. The aqueduct was patent although the ependyma was disrupted. In the midbrain, the region below the aqueduct showed maximal involvement, whereas the cerebral peduncles were relatively well preserved with good myelination and few Rosenthal fibres.

Involvement was maximal below the fourth ventricle in the pons and medulla. The nuclei of the basis pontis had more severe Rosenthal fibre accumulation than the white matter and the latter showed mild demyelination. In the medulla, the pyramids were less affected than the dorsal white matter and periolivary regions. In the cerebellum, severe Purkinje and granule cell loss was present in association with Bergmann gliosis. Rosenthal fibre formation and demyelination occurred only in the deep white matter, sparing the cortex and adjacent white matter.

In the spinal cord, both grey matter and white matter were severely affected and demonstrated prominent perivascular and subpial Rosenthal fibre formation. Demyelination was most marked in the anterior and lateral columns. The optic nerve showed fibre formation and patchy demyelination close to the chiasma but was spared distally. The retina and pituitary were normal.

At all levels of the neuraxis, the degree of demyelination was generally proportional to the extent of Rosenthal fibre formation. Neurons were preserved and gliosis was mild. Axon loss was commensurate with the degree of demyelination.

Case 4

K.R. was born at 43 weeks gestation by caesarean section because of failed induction. No fetal or neonatal distress was recorded.

At 4 weeks of age the infant became increasingly drowsy, was irritable when awake, fed poorly, began vomiting and lost weight. She was admitted to hospital at 10 weeks of age because of failure to thrive. Her height was 58 cm (75th centile), weight 3.65 kg (< 3rd centile) and head circumference 38.5 cm (50th centile). Neurologically, she was alert and active. The sucking reflex was almost absent and she had poor head control, generalized hypertonia and bilateral extensor plantar responses. An EEG was normal. Isotope brain scanning showed a marked increase in tracer distribution in the frontal lobes. Unenhanced computerized tomography (CT) scanning showed diffuse enlargement of the ventricles. With contrast, a marked blush was seen in the basal ganglia extending into the centrum ovale.

At 14 weeks of age, a brain biopsy was performed. Postoperatively, progressive hydrocephalus developed and a left ventriculoperitoneal shunt was inserted. She was discharged and her condition deteriorated over the ensuing three months with progressive physical disability and persistent seizures.

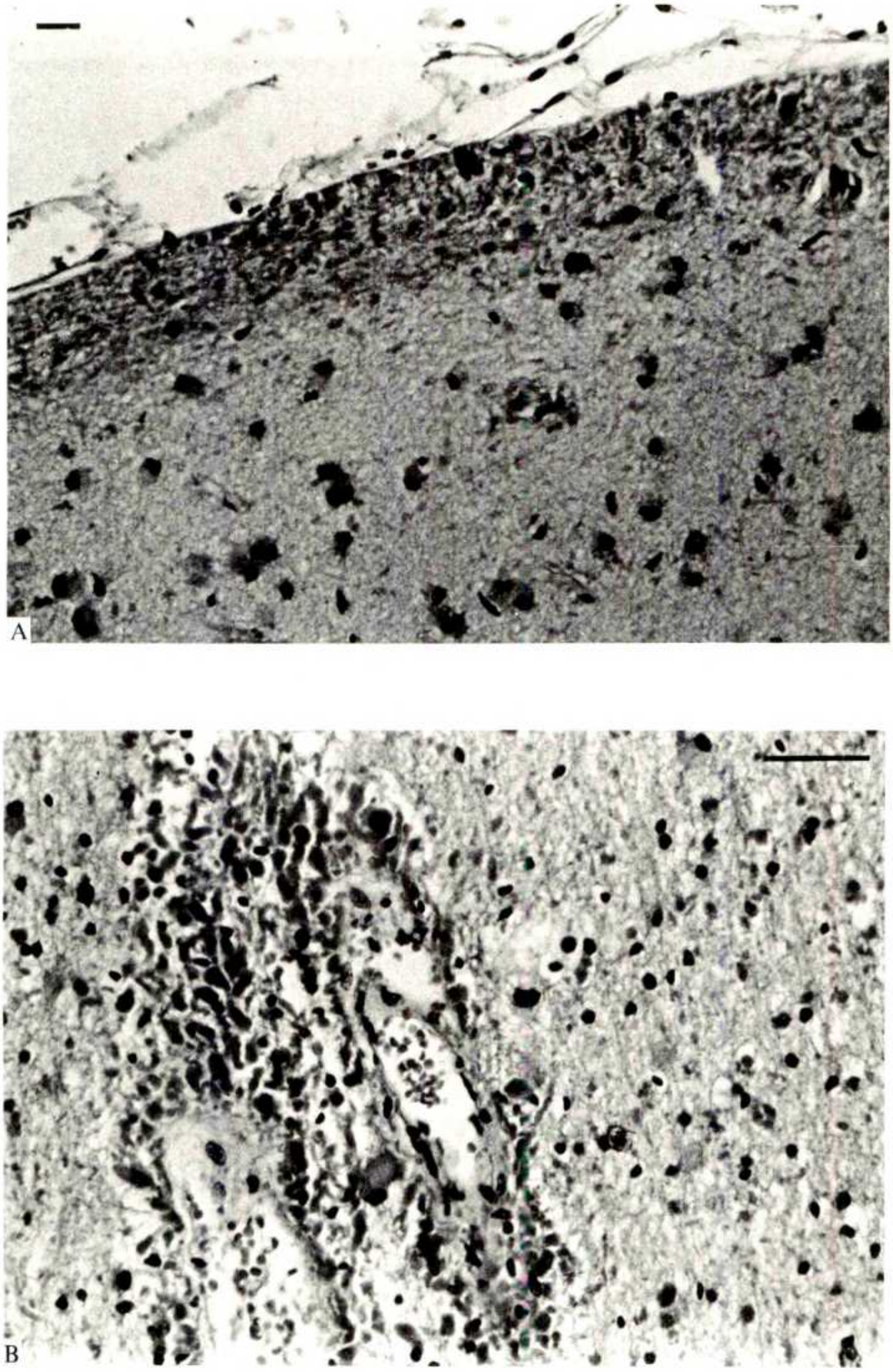

FIG. 2. Rosenthal fibre accumulation in subpial (A) and perivascular (B) locations. Luxol fast blue. Bars = 100 μm.

Eventually she was unable to tolerate any feeds and active support was discontinued. She died at 7 months of age.

The right frontal brain biopsy measured 2.5 × 3.0 × 1.5 cm and contained grey and white matter. No gross abnormalities were present. The most prominent histological feature was the many large astrocytes whose cytoplasm was distended by eosinophilic refractile granules (fig. 3A). The nucleus was often displaced to the periphery by the intracytoplasmic inclusions. Binucleate and multinucleate forms were present. These astrocytes were far more frequent in the white matter, although in some areas the cortex was infiltrated throughout. Several mitoses were identified in the white matter and cortex. Extensive demyelination and axon loss were present in the white matter and reactive astrocytes in the white matter and subpial region. Rosenthal fibres were identified with difficulty in the subpial region.

Electron microscopy showed that many astrocytes contained skeins of glial filaments surrounding osmiophilic deposits in the perikaryon, displacing organelles, especially mitochondria, to the periphery of the cell. Within the network of filaments, irregular electron-dense masses of various sizes were identified. They were not membrane-bound and many seemed to have a fibrillar background that was continuous with the surrounding glial filaments. Astrocytic processes were distended with similar but smaller aggregations of glial filaments. Perivascular astrocytic foot processes were affected. There appeared to be an increase in pinocytotic vesicles within endothelial cells but there was no disruption of the cell junctions.

At autopsy the brain in the fresh state weighed 717 g (normal = 700 g) and no gross abnormalities were seen. Coronal sections of the hemispheres 1 cm thick revealed a large parenchymal defect at the site of the right frontal biopsy. The centrum semiovale in the region of the frontal lobe was retracted, granular and slightly yellow. These changes were most prominent in the anterior portions of the frontal lobes and less marked in the posterior portions. Gross changes were absent in the parietal, temporal and occipital lobes. The lateral and third ventricles were markedly dilated. Coronal sections of the brainstem showed no abnormality, apart from aqueductal stenosis, and sections of the cerebellum and spinal cord were normal.

In the cerebral hemispheres, Rosenthal fibres were most prominent in the subpial and periventricular regions and cystic degeneration of the white matter was present. As in the biopsy specimen, there was increased cellularity owing to the presence of large granular astrocytes. Mature Rosenthal fibres were infrequent in the centrum ovale, whereas small introcytoplasmic refractile granules were abundant. Scattered calcospherites were present in the white matter.

In the cortex, neurons were preserved apart from an occasional karyorrhectic cell, atypical astrocytes were absent and a small number of refractile granules resembling small Rosenthal fibres were seen. The frontal regions were more involved than the occipital lobe. Demyelination occurred in proportion to the degree of astrocytic changes and was accompanied by axonal loss. In the thalamus and basal ganglia, the

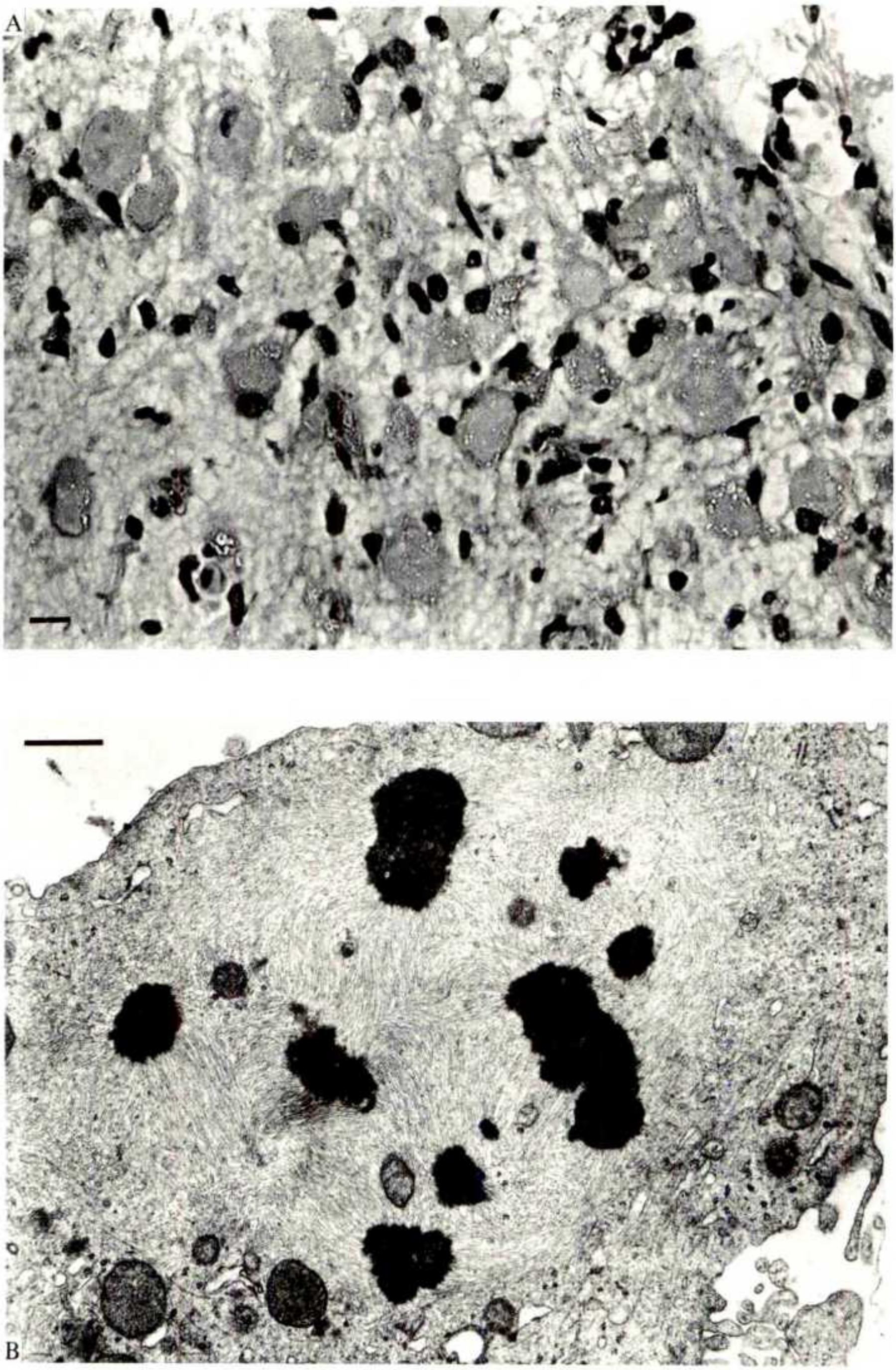

FIG. 3. Early stage of Alexander's disease. A, Rosenthal fibres appearing as small granules within the cytoplasm of astrocytes. Haematoxylin and eosin. Bar = 10 μm. B, electron micrograph of the granules, which appear as small osmiophilic densities. Electron micrograph. Bar = 1.0 μm.

changes were most prominent in the subependymal region and decreased with increasing distance from the ventricular surface. As in the deep white matter, increased cellularity was evident. Nuclear groups and white matter tracts were equally involved and a prominent perivascular inflammatory reaction was present.

Changes in the brainstem were maximal in the subpial region and tegmentum and reflected those in the hemispheres. In the midbrain, the aqueduct was almost occluded secondary to the proliferation of atypical astrocytes. The substantia nigra and cerebral peduncles showed less severe changes and the nuclear groups and fibre tracts in the basis pontis were equally involved. The tegmentum below the ventricle and the periolivary region showed severe changes. Demyelination was prominent in the pyramids and less marked in the medial lemnisci.

In the deep nuclei and white matter of the cerebellum, changes were similar to those in the cerebral hemispheres. Perivascular inflammatory infiltrates were seen in the affected areas and the cerebellar cortex and underlying white matter were spared. The spinal cord showed prominent subpial and perivascular Rosenthal fibre deposition. Similar changes were seen in the white matter, although the grey matter showed a paucity of atypical granular astrocytes. Demyelination was most extensive in the anterior and lateral columns. As in previous cases, neurons were preserved and gliosis was mild.

Case 5

P.P. developed normally until 7 months of age, when a plateau was reached. At 1 year of age, loss of milestones began. Head enlargement was noted at 15 months and a febrile convulsion occurred at 18 months. A right ventriculoperitoneal shunt was inserted six months later.

At 34 months of age, the child was referred to The Hospital for Sick Children after a second febrile convulsion. Her height was 81 cm (3rd centile), weight 11 kg (3rd centile) and head circumference 52.8 cm (> 98th centile). She was unable to sit unsupported and had no recognizable words. Vision was grossly intact. At rest, the legs were adducted and the left arm was dystonic and held in flexion. She had no functional use of this limb. Bilateral papilloedema was present. The remaining cranial nerves were intact. She had a mild spastic quadriparesis with hyperreflexia and bilateral extensor plantar responses. CT scanning showed mild to moderately dilated ventricles and an overall low density of the white matter. There was modest subcortical and cortical enhancement with contrast (fig. 4). An EEG showed an excess of slow-wave activity, which was more prominent on the left. A brain biopsy was performed.

The right frontal surgical biopsy measured 1 × 0.5 × 0.4 cm and contained grey and white matter. No gross abnormalities were seen. Striking Rosenthal fibre accumulation was seen in the subpial and perivascular regions. Numerous fibres were also scattered throughout the neuropil of the grey and white matter, although they were more numerous in the latter. Many astrocytes were present whose cytoplasm was distended with small refractile eosinophilic granules. Typical reactive astrocytes were seen, particularly in the white matter. Demyelination was prominent and was accompanied by axonal loss. Several glial nodules were identified in the cortex and scattered calcospherites were seen in the grey and white matter.

Electron microscopy showed typical Rosenthal fibres (fig. 5). Astrocytes were

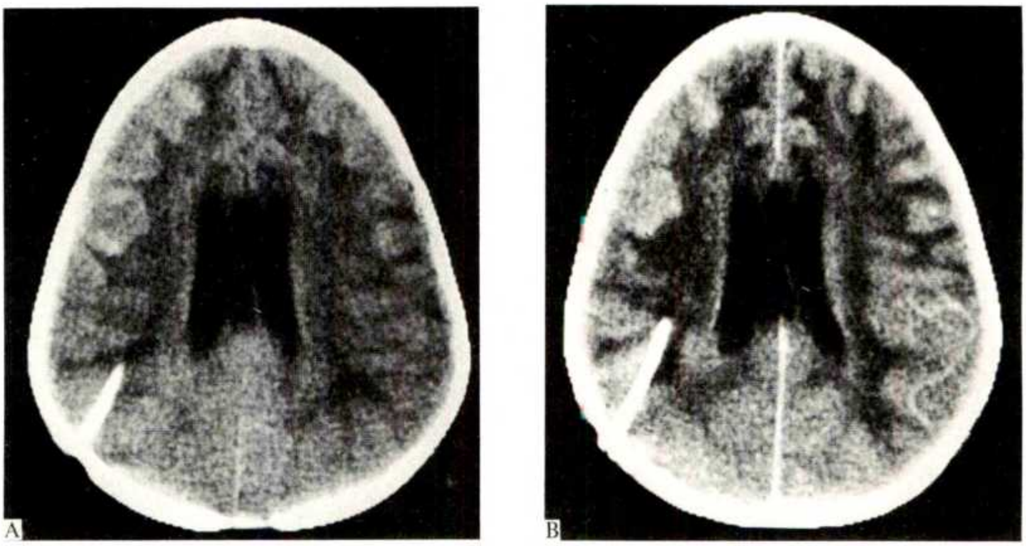

FIG. 4. Unenhanced (A) and enhanced (B) computerized tomographs showing cortex and subcortex.

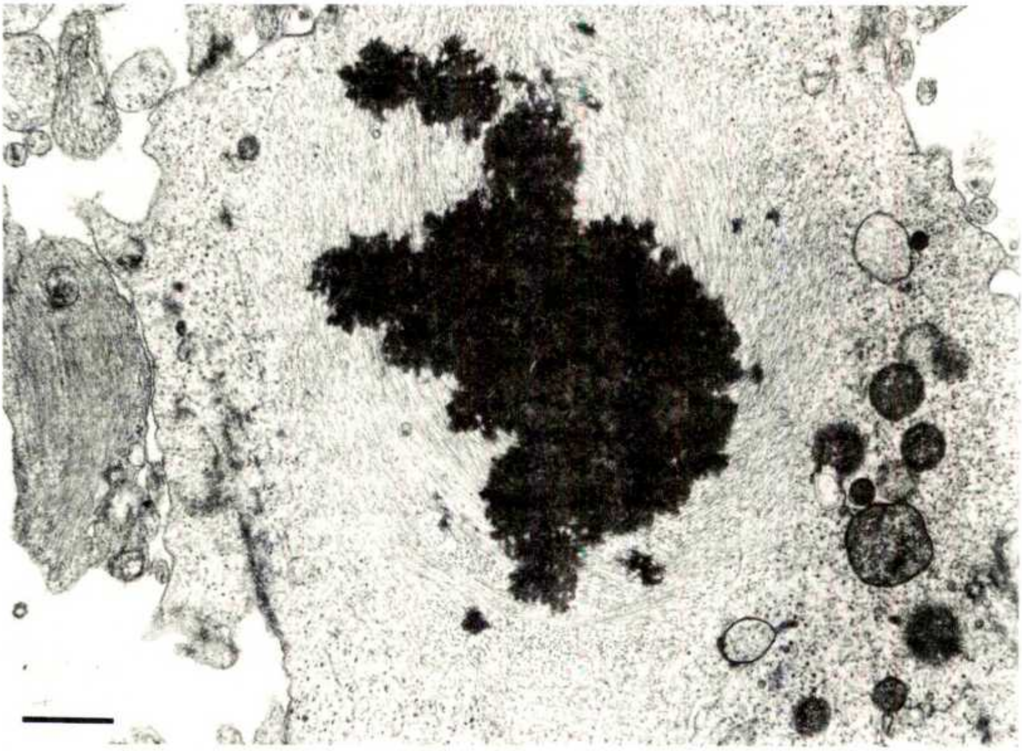

Fig. 5. Rosenthal fibres. The larger more mature fibre consists of a centre of osmiophilia surrounded by a network of intermediate filaments that appear to merge with the centre. Electron micrograph. Bar = 0.5 μm.

identified with cytoplasm packed with glial filaments containing small irregular electron-dense masses. Numerous myelin figures were present in these cells.

Case 6

D.H. developed normally until the age of 14 years when he began complaining of leg weakness. The disability progressed until the age of 17 by which time leg spasticity had confined him to a wheelchair. Arm weakness, limb ataxia and diplopia on downgaze evolved concurrently. His neurological state deteriorated progressively and he became dysarthric, dysphagic and doubly incontinent and was dyspnoeic at rest. He died from pneumonia when aged 23 years.

On examination during the week before death his mental state was normal, his speech was slurred, and vertical and horizontal gaze-evoked nystagmus was present. Pyramidal weakness was moderate in his arms and marked in the legs. The reflexes were brisk and the plantar responses extensor. Limb ataxia was demonstrable in the arms. Sensory examination was normal.

At autopsy the brain in the fixed state weighed 1475 g and was grossly normal. Coronal sections of the cerebral hemispheres were normal. Transverse sections through the brainstem and cerebellum showed atrophy of the pyramids and a granular appearance of the dentate nuclei. The spinal cord showed generalized atrophy.

In the cerebral hemispheres, scattered Rosenthal fibres were seen in the subpial regions and the cortex was well preserved. The subcortical white matter showed mild demyelination in association with reactive astrocytes and mild Rosenthal fibre deposition. The changes were more marked and in the deeper part of the hemispheres fibre formation was maximum in the subependymal region. The nuclear groups of the thalamus and basal ganglia showed scattered Rosenthal fibres, whereas the deposition was most intense in the internal capsule. The latter demonstrated mild to moderate demyelination.

In the midbrain, the tegmentum around and ventral to the aqueduct was the site of maximal involvement with relative sparing of the brachium conjunctivum, substantia nigra and cerebral peduncles. This distribution was reiterated in the pons where the tegmentum below the fourth ventricle showed the most striking Rosenthal deposition and demyelination. In the basis pontis, grey and white matter were equally affected and the latter showed very mild, patchy demyelination.

Very intense Rosenthal fibre deposition and demyelination were present in the medulla with the dorsal tegmentum and pyramids showing the severest involvement. Perivascular mononuclear infiltrates were also seen in the medulla. The deep cerebellar nuclei and white matter showed severe fibre deposition and demyelination. The changes were less marked near the cortex. Numerous torpedoes were seen in the superficial granular layer and scattered fibres were present in the subpial region.

In the spinal cord, Rosenthal fibres had a perivascular and subpial distribution and were seen throughout the grey and white matter. Demyelination was most severe in the anterior and lateral columns although the fasciculus gracilis showed mild involvement. The optic nerves also showed patchy demyelination and scattered fibres.

Throughout the neuraxis, neurons were well preserved and demyelination generally was commensurate with the degree of Rosenthal fibre formation.

IMMUNOPEROXIDASE STAINING

Representative sections from all cases underwent immunoperoxidase staining according to the method of Sternberger *et al.* (1970). The following antisera and dilutions were used: antifibrinogen (1:50), anti-pooled immunoglobulin (1:2000), antialbumin (1:50), antikeratin (1:400), anti-S100 (1:400) and anti-GFAP (1:200) (fig. 6A).

Rosenthal fibres showed no immunolabelling with any of the antisera. In Case 4, the cytoplasm of the large granular astrocytes showed positive immunostaining with anti-GFAP. Within the dense cytoplasmic staining, small areas of negative staining were seen that corresponded to the immature Rosenthal fibres (fig. 6B).

DISCUSSION

Since Alexander's (1949) original description of fibrinoid degeneration of astrocytes as a cause of progressive neurological deterioration, isolated cases showing a similar pathological picture have been reported (Stevenson and Vogel, 1952; Crome, 1953; Stevenson, 1957; Wohlwill *et al.*, 1959; Vogel and Hallervorden, 1962; Friede, 1964; Herndon and Rubinstein, 1968; Peiffer, 1968; Schochet *et al.*, 1968; Seil *et al.*, 1968; Herndon *et al.*, 1970; Sherwin and Berthrong, 1970; Kepes and Ziegler, 1972; Tihen, 1972; Mastri and Sung, 1973; Garret and Ames, 1974; French *et al.*, 1976; Russo *et al.*, 1976; Cole *et al.*, 1979; Habib *et al.*, 1984).

Russo *et al.* (1976) recently reviewed the literature and emphasized the presence of three clinical subgroups. The first consists of the infantile group, which includes Alexander's original patient. Onset of symptoms is from birth to early childhood and the course is one of inexorable neurological deterioration with psychomotor retardation, seizures, quadriparesis and megalencephaly. The average duration of the illness is 2½ years.

The juvenile group has an onset of symptoms from 7 to 14 years of age. The course is characterized by progressive bulbar symptoms and spasticity. Seizures and cognitive deterioration are less prominent and the average duration of the illness is 8 years.

The adult cases comprise the third group. Onset of symptoms may occur between the second and seventh decades. Clinically, these adults, whose pathological picture is similar to that of the infantile and juvenile groups, may have a course consistent with classical multiple sclerosis or may be asymptomatic.

The pathological hallmark of all subgroups is the diffuse accumulation of Rosenthal fibres, particularly in the subependymal, subpial and perivascular regions. Demyelination is extensive in the infantile cases, less severe in the juvenile group and variable in the adults. Neurons are invariably well preserved.

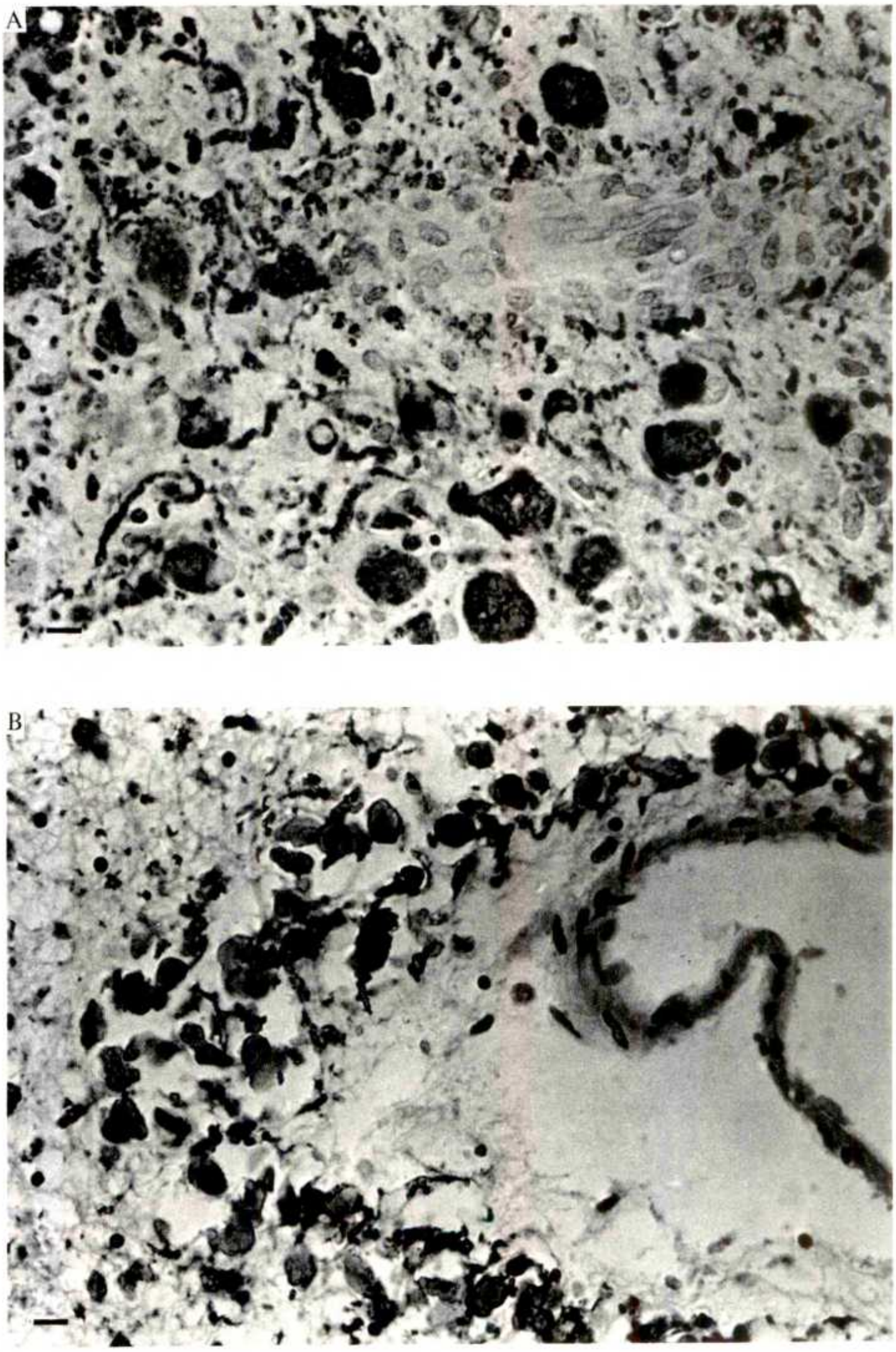

FIG. 6. Rosenthal fibres. A, granules in a young patient, most of which show a small central area of negativity with antisera to glial fibrillary acidic protein. B, large irregular masses are negative when stained with antisera to glial fibrillary acidic protein. Positivity surrounding the negative areas is characteristic. Immunoperoxidase reaction. Bar = 10 μm.

More recently, changes characteristic of Alexander's disease but localized to the medulla and upper cervical cord have been described in a child and an adult (Soffer and Horoupian, 1979; Goebel *et al.*, 1981). Whether this represents localized Alexander's disease or simply exemplifies a similar histopathological reaction of astrocytes in the face of a different pathogenetic mechanism is uncertain. Clearly the nosology of these syndromes is not known. Until further information is obtained regarding the specific abnormality leading to Rosenthal fibre formation, we prefer to reserve the term Alexander's disease to cases with the diffuse and characteristic deposition of Rosenthal fibres described in the original paper.

In our series of infantile and juvenile cases, the pathology and pathological idiosyncrasies were so similar that the implication that they represent the same disease is inescapable. Rosenthal fibres accumulate predominantly in the subpial, perivascular and subependymal region. Extensive demyelination occurs in the cerebral hemispheres with the deep white matter being most severely affected. The cortex is invariably well preserved with little Rosenthal fibre formation. In the thalamus and basal nuclei, the opposite pattern is frequently seen with the grey matter incurring the most fibre formation. Neurons are preserved regardless of the degree of Rosenthal fibre deposition.

The periventricular region is most severely affected with involvement decreasing as distance from the ependymal surface increases, and the frontal region is more involved than the occipital region. In the brainstem, the tegmentum, particularly the periaqueductal and subventricular region, is the site of maximal Rosenthal fibre formation. The involvement of the nuclei in the basis pontis may or may not exceed that in the corticospinal and pontocerebellar tracts. Involvement is more marked in the medulla than in the rostral brainstem. The cerebellar cortex is remarkably spared with the deep nuclei and white matter suffering extensive involvement.

The grey and white matter of the spinal cord are equally affected with the latter showing maximal demyelination in the lateral and anterior columns. Rosenthal fibre formation is most marked in the proximal optic nerves and is associated with patchy demyelination.

Case 4 illustrates the pathological changes in an infant who came to biopsy at 14 weeks of age. Mature Rosenthal fibres were found only with difficulty. The striking abnormality in the biopsy was the presence of large numbers of atypical astrocytes with distended cytoplasm filled with small, refractile granules showing the typical ultrastructure of Rosenthal fibres. Skeins of glial filaments formed masses in the centre of the astrocytic perikaryon, displacing organelles to the periphery of the cell. Rosenthal fibres were scattered throughout these filamentous masses and myelin figures were conspicuous in some cells.

It is conceivable that this disruption of normal cytoplasmic architecture would lead to further derangements in astrocytic function. The presence of these changes in astrocytic foot processes may be related to the disruption of the blood-brain barrier seen in the region of the basal nuclei on CT scanning. Towfighi *et al.* (1983) reported no endothelial fenestrations or open junctions, although they also observed an increase in pinocytic vesicles within the endothelial cells. Nuclear atypia was common in these astrocytes and mitoses were evident in the grey and white matter.

In the autopsy at 7 months of age, Rosenthal fibres had formed in the subpial, subependymal and perivascular regions. The large granular astrocytes were still present but not as prominent. Increased cellularity due to the presence of these atypical astrocytes, present in the hemisphere in the biopsy, was seen in the hemispheres, brainstem and cerebellum in the autopsy.

The finding of increased cellularity due to atypical, granular astrocytes has been previously reported and has been interpreted as neoplastic (Sherwin and Berthrong, 1970; French *et al.*, 1976). Infiltration of meninges by these astrocytes may occur, further suggesting a neoplastic process. The increased cellularity secondary to the atypical astrocytes has only been described in infants less than 1 year of age. It is uncertain whether this reaction is idiosyncratic to the maturing brain of the infant or is the initial astrocytic abnormality in all cases of Alexander's disease. Certainly, hypercellularity is not conspicuous in most biopsies or autopsies from cases of Alexander's disease. The assumption that proliferation of morphologically atypical astrocytes occurs early in the course of the illness and is followed by progressive astrocyte death, leaving a normocellular neuropil containing abundant Rosenthal fibres as the only morphological indication of an astrocytic abnormality, would explain several features of the disease. It has been assumed that the megalencephaly in infantile Alexander's disease is secondary to massive deposition of Rosenthal fibres in the brain parenchyma. However, proliferation of atypical astrocytes is conceptually more plausible. The subsequent atrophy of the brain would be secondary to progressive astrocyte cell death in association with the loss of non-astrocytic cell lines occurring as a result of the primary astrocytic abnormality.

The syndrome of pseudotumour cerebri in Case 1 is relevant as a consequence of this proposed evolution. Conceivably, the absence of raised intracranial pressure in most affected juveniles and adults may be secondary to the slow evolution of the disease, which prevents accumulation of large numbers of astrocytes. The presence of scattered astrocytes with distended cytoplasm filled with eosinophilic granular deposits in most reported cases of Alexander's disease may represent the only indication of this process.

Alexander's disease is generally reported as a leucodystrophy rather than a primary, nonneoplastic disease of astrocytes. However, accumulation of Rosenthal fibres is the most conspicuous pathological abnormality in the disease. These fibres may be more numerous in the grey matter than the white matter, particularly in the basal ganglia, thalamus and brainstem. Although the degree of demyelination in the white matter is usually proportional to the severity of Rosenthal fibre deposition, areas are seen in which fibre formation is extensive despite the absence of significant demyelination. Furthermore, proliferation of atypical, granular astrocytes seen in the infantile cases has not been observed in any known pathological process.

An abnormality of astrocyte function could lead to diverse functional and pathological consequences. Developmentally, astrocytes or, more specifically, radial glia, aid neuronal migration from the periventricular matrix to the cerebral and cerebellar cortices. They provide structural support for the nervous system and are central to regenerative repair. Astrocytic foot processes provide physical and electrical insulation for synapses, preventing activity at one synapse from influencing the excitability of neighbouring synapses.

The role of astrocytes as potassium sinks is well established (Hertz, 1978). Functionally, they prevent accumulation of potassium in the extracellular space during neuronal activity. The active role of astrocytes in uptake, turnover and metabolism of the amino acid transmitters glutamate and GABA is well established and has been intimated with respect to adenosine, noradrenaline and serotonin. Finally, astrocytes may provide a reservoir for nutrients and have been implicated in the molecular biology of memory (Kuffler and Nicholls, 1976; Varon and Somjen, 1979).

Astrocytes are obviously integral to a number of neural functions and two immediate questions arise with respect to the consequences of the astrocytic abnormality in Alexander's disease. The first concerns the mechanism of demyelination secondary to astrocytic dysfunction. The second relates to the factors responsible for the severity and rapid course in the maturing infantile nervous system.

Details of oligodendrocyte-astrocyte interactions are scanty. Gap junctions between astrocytes and oligodendrocytic cell bodies or processes (Massa and Mugnaini, 1982) provide a means of metabolic cooperation facilitating transfer of ions and molecules (Goodenough, 1980). Functionally, this interaction may be a prerequisite for the acquisition and maintenance of the myelin sheath.

In experimental animals, it has been postulated that absence of astrocytes may prevent oligodendrocytes from remyelinating surrounding axons. These studies, using intraspinal injections of 6-aminonicotinamide (6-AN) in the rat and intraspinal injections of lysolecithin in the rabbit to produce demyelination and astrocyte death, suggest that astrocytes represent the 'third factor' to allow oligodendrocytes to myelinate signalling axons (Blakemore, 1981).

In the immature developing nervous system, the effect of an astrocytic abnormality depends on the stage of gliogenesis. The problem is complicated by the lack of details as to the ontogeny of astrocytes and oligodendrocytes. Prenatally, GFAP-positive cells are present in the periventricular matrix in the first third of gestation in the Rhesus monkey (Levitt *et al.*, 1981). They are the origin of the radial glial fibres. Thus, when GFAP is used as a specific marker for developing glia, astrocyte precursors are seen to appear early in the developing brain.

In the rat, optic nerve astroblasts and oligodendroblasts (as defined by electron microscopy) and not undifferentiated glioblasts are the major sources of mature astrocytes and oligodendrocytes (Skoff *et al.*, 1976*a*, *b*). Most astrocytes and all oligodendrocytes undergo their final cell division postnatally. In the rat optic nerve, the astroblasts can be traced to ventricular cells in the early prenatal period, which would correspond to the GFAP-positive cells in the same region in the monkey. The origin of oligodendroblasts is less certain since they appear rather suddenly about two days postnatally in the rat (Skoff *et al.*, 1976*a*, *b*).

Myelination glia are positive when immunolabelled with anti-GFAP serum (Takashima and Becker, 1983). Oligodendrocytes may evolve from astroglia precursors: if this is the case, a defect that manifests at or near birth could affect both astrocytes and oligodendrocytes and may explain the severity of Alexander's disease in infantile cases. Electron microscopic examinations of our case material did not reveal an abnormality of oligodendrocytes. However, Towfighi *et al.* (1983) have described aberrant myelination of astrocytic processes.

The nature of the defect in Alexander's disease is unknown. Because of the massive accumulation of Rosenthal fibres, attention has focused on these structures in an attempt to elucidate the specific astrocytic dysfunction. Since Rosenthal (1898) described focal formation of these hyaline deposits in a case of syringomyelia, it has become evident that they also occur in a variety of conditions including astrocytomas and in areas of long-standing gliosis around craniopharyngiomas, ependymomas and in the plaques of multiple sclerosis (Herndon *et al.*, 1970).

Ultrastructurally, Rosenthal fibres consist of an irregular electron-dense mass with distinct margins but no limiting membrane. They are always associated with skeins of dense glial filaments that appear to enter and exit from the masses. Their chemical composition is unknown. Herndon *et al.* (1970) suggested they are related to an abnormality in production and/or degradation of glial filaments that results in an accumulation of degenerative products related to the electron-dense masses.

Rosenthal fibres do not stain for GFAP but are surrounded by a rim of GFAP-positive cytoplasm (Janzer and Friede, 1981). If they are a degenerative product of glial filaments, their formation must be associated with a change in their chemical composition or reactivity. In the rat, Horoupian *et al.* (1982) showed strong immunolabelling of nickel implant-induced Rosenthal fibres with antialbumin serum. They suggested that in this particular model, exudation of plasma proteins and subsequent pinocytosis by astrocytes leads to intracellular accumulation in the form of these fibres. We found the fibres did not show immunolabelling with antialbumin, antiglobulin or antifibrinogen serum. Staining was negative also for keratin, S100 protein and GFAP.

Clearly, many questions remain unanswered. Although the clinical picture and pathology in this condition are established, hypotheses rather than facts prevail when pathogenetic mechanisms are discussed. The paucity of knowledge concerning astrocyte metabolism, astrocyte-neuron relationships and astrocyte-oligodendroglia interactions compound the problem. Alexander's disease is unique in that it represents a nonneoplastic disease of astrocytes and as such has a valuable role in the understanding of human astrocyte dysfunction.

ACKNOWLEDGEMENT

This manuscript was prepared with the assistance of the Medical Publications Department, The Hospital for Sick Children, Toronto, Ontario, Canada.

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(*Received July 17, 1984. Revised October 4, 1984. Accepted October 10, 1984*)

Brain (1985), 108, 387-404

TYMPANIC MEMBRANE SENSATION

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SUMMARY

Sensation from the tympanic membrane is generally believed to be mediated *via* at least four cranial nerves, some authors describing discrete territories for each of these nerves. The lack of critical evidence for independent sensory areas prompted a clinical study of tympanic membrane sensation in 32 patients having known cranial nerve deficits. Tympanic membrane sensation was tested in four quadrants using a 300 mg bristle under a Zeiss operating microscope. The findings were highly suggestive of a predominantly nociceptive system. Any change relative to the opposite tympanum was usually anaesthesia. No complete trigeminal deficit retained perception in all tympanic quadrants. Facial, glossopharyngeal and vagal deficits alone never affected tympanic sensation. These findings support the trigeminal nerve as the principal sensory nerve to the tympanic membrane, supplemented only inconstantly and incompletely by the other cranial nerves.

INTRODUCTION

Although deep ear sensation is unquestionably mediated *via* several nerves (Hovelacque and Rousset, 1922; Cunningham, 1964; Brodal, 1965; Gray, 1980), it is uncertain if discrete local territories exist. Descriptions vary from depicting all sensations as trigeminal (Krieg, 1953) to graphic illustration of precise territories for each of several nerves (Testut and Latarjet, 1930; Graves and Edwards, 1944; Haymaker, 1969) (fig. 1). Since this uncertainty prevails largely from a lack of orderly charting of each nerve in question, we wish to describe the sensory findings in the deep ear in a series of patients having known deficits of the trigeminal nerve, nervus intermedius and glossopharyngeal and vagus nerves, separately and in combination. Our findings support the trigeminal nerve as the principal sensory nerve to the tympanic membrane.

MATERIAL AND METHODS

Thirty-two patients with a variety of surgical and neoplastic cranial nerve deficits were examined (Tables 1 and 2). Using a Zeiss operating microscope the tympanic membrane was examined in quadrants with a soft bristle calibrated at 300 mg. The ear with the suspected neurological deficit was examined first and compared with the normal side. If any inconsistencies were present, retesting was performed until reliable results were obtained.

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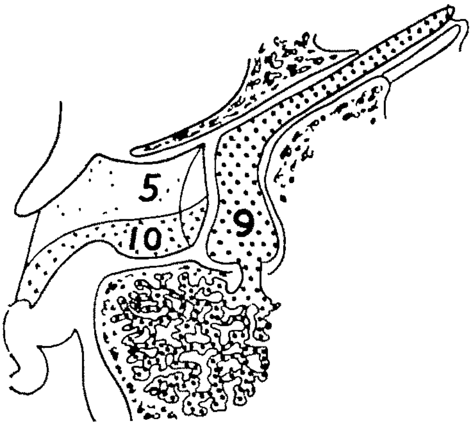

FIG. 1. Two authors' depiction of external ear territories. (Graves and Edwards (1944) The eustachian tube. *Archives of Otolaryngology*, **39**, 359–397. Reprinted with permission of publisher.)

Testing of the tympanic membrane with the bristle began in the posterior-superior quadrant, followed by the posterior-inferior, anterior-inferior, and anterior-superior quadrants. The patient was asked to respond 'yes' when a sensation was felt. If there was no response, the drum was touched several times in succession but only hard enough to discern a barely perceptible bend in the bristle or indentation in the membrane. The patient was asked to discriminate carefully between 'hearing' and 'feeling' the bristle. This was particularly important for patients with unilateral hearing loss.

After the tympanic membrane was tested, progression was made to the adjacent skin of the external auditory canal. Again, testing began in the posterior-superior quadrant and continued around to the anterior-superior quadrant. Before testing, the canal skin was meticulously debrided. Again, the patient was asked to discriminate between hearing and feeling the bristle. We found that some patients with neurologically intact canals could not feel a bristle calibrated at 300 mg in any quadrant but could feel a fine steel ear pick gently applied to the ear canal skin. Comparisons were made first by bristle and then by pick.

Our clinical material included patients with trigeminal neuralgia (10), primary otalgia (8), glossopharyngeal neuralgia (3), vascular headache (1), hemifacial spasm (2), acoustic neurinoma (5), trigeminal neurinoma (1), glossopharyngeal neurinoma (1) and extradural jugular foramen hamartoma (1).

Patients with fifth nerve (10), seventh nerve (11), ninth nerve with the two upper rootlets of the tenth nerve (2) and ninth nerve with complete tenth nerve (4) dysfunction were studied. No isolated defects of either the ninth or tenth nerve were studied. The remaining evaluations, creating a total of 35 different mappings, had combinations of trigeminal, total seventh and eighth nerve (1), trigeminal, total facial, eighth, ninth and tenth nerves (3) and sensory facial, ninth and partial tenth nerves (4). The trigeminal

TABLE 1. CASE MATERIAL—32 PATIENTS

Trigeminal neuralgia	10
Primary otalgia	8
Glossopharyngeal neuralgia	3
Vascular headache	1
Acoustic neurinoma	5
Trigeminal neurinoma	1
Hemifacial spasm	2
Glossopharyngeal neurinoma	1
Extradural jugular foramen tumour	1

neuralgia patients had been treated by posterior fossa sensory root section, displacement of a compressing superior cerebellar artery, or injection of glycerol into Meckel's cave. Case summaries are provided in Tables 3–7. (For Tables 3–10, *see* Appendix.)

It should be acknowledged that sensory observations on the skin of the ear canal lack the definitiveness of the tympanic examination. A variability of stimulus and response was a distinct concern when testing in the canal. Bristle contact with the tympanum, on the other hand, nearly always elicited a noxious response or anaesthesia. For this reason, we feel our more reliable observations are those concerning the tympanum.

TABLE 2 CRANIAL NERVE DEFICITS TESTED—35 STUDIES

Trigeminal (neuralgia 9, trigeminal neurinoma 1)	10
Facial sensory (nervus intermedius section for otalgia 7, vascular headache 1)	8
Facial sensory possible (hemifacial spasm)	1
Motor and sensory facial (small acoustic tumours)	2
Glossopharyngeal and incomplete vagus (glossopharyngeal neuralgia)	2
Glossopharyngeal and complete vagus	4
Trigeminal and motor and sensory facial, acoustic (trigeminal neuralgia)	1
Trigeminal, motor and sensory facial, acoustic, glossopharyngeal and vagus (giant acoustic tumours)	3
Facial sensory, glossopharyngeal and two vagal rootlets (otalgia)	4

Scarring or other structural pathology of the drum often resulted in focally decreased sensation. Such cases were therefore not included in this study. Most cases were examined prior to surgical discharge and at least one further time over a six month period. Sensory deficits were fixed after the immediate postoperative period. Preoperative examinations were often done but are not a principal aspect of this report. The latest examination is tabulated.

RESULTS

We found the Zeiss operating microscope indispensible for bristle examination of the tympanum and the posterior canal. Sharp probe use just peripheral to the membrane was impossible without the microscope. Indeed, we have to question the reliability of mapping reported before the use of the surgical microscope. A cough reflex was occasionally noted with tympanum stimulation. An unpleasant or frankly painful sensation was consistently noted with tympanic stimulation in those with intact sensation.

The tympanic membrane sensation was always normal when the trigeminal nerve was intact. Commonly, if any trigeminal deficit was present the tympanum was partly or totally anaesthetic. Of 14 patients with trigeminal nerve disturbance isolated or in combination, 6 had normal tympanum sense (4 of whom were in the glycerol treatment group) and 1, a patient with a large acoustic neurinoma, had preoperative tympanum anaesthesia. Fig. 2 illustrates the 7 cases with postoperative anaesthesia of the tympanum. All had trigeminal nerve lesions.

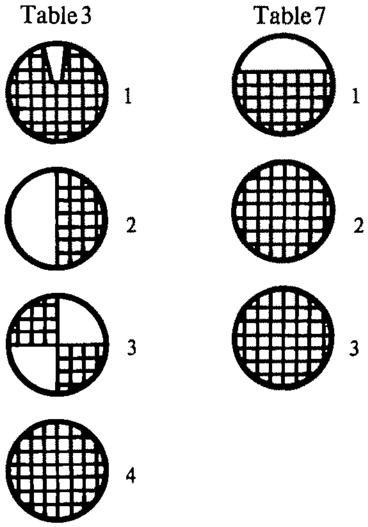

FIG. 2. Patterns of tympanic membrane anaesthesia from Tables 3 and 7. All involve the trigeminal nerve. (Cross-hatched areas represent sensory change.)

Of the nontrigeminal cases there was none with tympanic sensory loss; one, however, had an area of hypersensitivity when compared with the opposite ear (Case 10, Table 4, small acoustic neurinoma). Two tympanic membranes with sensory change manifested hypaesthesia rather than anaesthesia (Case 7, Table 3, glycerol injection, and Case 4, Table 7, a patient with an acoustic tumour who preoperatively had tympanum anaesthesia). Fig. 2 illustrates the extent of the hypaesthesia in these 2 cases. All tumours involving the trigeminal nerve directly or indirectly had tympanic findings (Table 7).

There were 11 pure seventh nerve deficits which included 8 cases with surgical section of the nervus intermedius and/or geniculate ganglionectomy. This subgroup had measured decreases in lachrimation and anterior tongue taste sensation for varying periods. None of the 11 cases had sensory loss of the tympanic membrane. There were 10 cases with partial or complete deficit of the vagoglossopharyngeal complex in conjunction with intact trigeminal nerves. None of these manifested any tympanic sensory change.

The deep canal findings were less definitive but again were more commonly observed in the trigeminal cases. Three nontrigeminal cases manifested canal changes, one small acoustic tumour, one hemifacial spasm, and one combined rhizotomy of nervus intermedius, glossopharyngeal and vagus nerves. Those cases

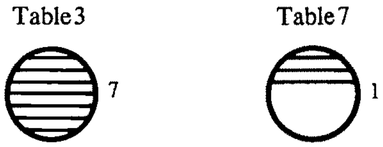

FIG. 3. Patterns of tympanic membrane hypaesthesia from Tables 3 and 7. Both involve the trigeminal nerve. (Horizontal lines represent areas of sensory change.)

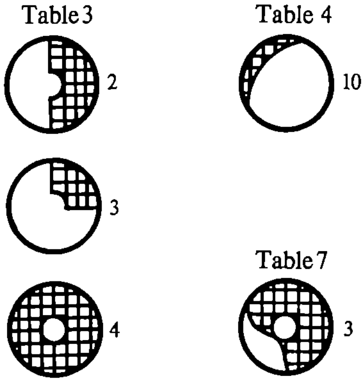

FIG. 4. Patterns of external canal anaesthesia from Tables 3, 4 and 7. (Cross-hatched areas represent sensory change. The central ring represents the tympanic membrane.)

with combination deficits had no consistent pattern beyond the trigeminal tympanic predeliction (figs. 4, 5).

DISCUSSION

We undertook this study with the impression that the territories in the deep ear had not been well defined. This had led, we believed, to conflicting and erroneous descriptions of discrete tympanic membrane territories for each of several nerves known to supply the ear. We found the trigeminal nerve to be the principal somatic

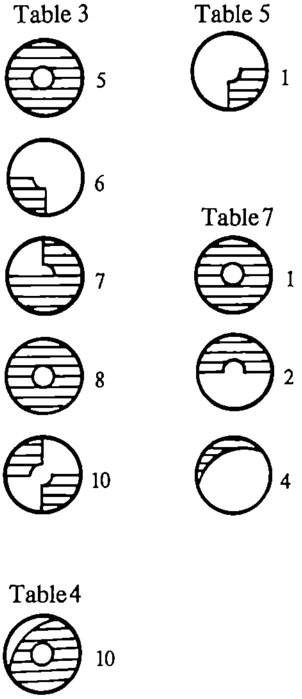

FIG. 5. Patterns of external canal hypaesthesia from Tables 3, 4, 5 and 7 (The central ring represents the tympanic membrane. Sensory change is marked by horizontal lines.)

sensory nerve to the tympanum. Complete trigeminal nerve loss always resulted in localized or generalized tympanic anaesthesia. Even partial trigeminal deficits often produced tympanic anaesthesia. Dysfunction of the nervus intermedius, glossopharyngeal and vagus nerves did not produce anaesthesia singly or in combination. We could demonstrate no tympanic sensory loss, regardless of the extent of denervation, if the fifth nerve remained intact. On the basis of these findings, we concluded that the trigeminal fibres must arborize throughout the entire tympanum and are supplemented only inconstantly and incompletely by the other nerves.

Wilson's (1911) tympanic membrane studies tend to support our conclusions. The examination of degeneration after sectioning the auriculotemporal nerve indicated that the tympanic nerves were largely trigeminal (Wilson, 1907). Wilson showed two routes of innervation: one by a large trunk entering across the pars flaccida (the posterior-superior drum), and the other by a corona of numerous small branches from the periphery. In noting the predominance of free nerve endings and neuroanatomical similarities to the cornea, Wilson stated '... as in the cornea pain and not touch appears to be the sensation evoked, so also in the membrane tympani one might expect that the slightest pressure would evoke unpleasant sensations passing into pain.' We were similarly impressed that stimulation of the tympanic membrane, with few exceptions, produced either pain or revealed anaesthesia.

Well before the era of surgical neurology, anatomical dissection suggested a somatic sensory role about the ear for the trigeminal (Bell, 1834), glossopharyngeal (Krause, 1866; Barbarisi, 1851) and vagus nerves (Arnold, 1840; Barbarisi, 1853). The ear was seen as being surrounded by the auriculotemporal (fifth) branch reaching the external canal anteriorly, Jacobson's nerve (ninth) penetrating directly to the tympanic cavity and the nerve of Arnold (tenth) approaching the canal posteriorly. The cutaneous component of the facial nerve was yet to be considered, but its aural proximity was inescapable.

Communications and connections among the several nerves were believed to exist. This neural overlap would cancel out any measurable effect of the loss of a single nerve (Stookey, 1928; Brodal, 1965). Bischoff (1865) had found communications between virtually all the lower cranial nerves and the upper cervical rootlets. Although extremely variable (Hovelacque and Rousset, 1922), at least four anastomoses are generally acknowledged today (Cunningham, 1964; Gray, 1980): the facial and vagus at their crossing in the facial canal, the auriculotemporal and facial in the substance of the parotid gland, the facial and glossopharyngeal by a filament between the geniculate ganglion and the lesser superficial petrosal nerve in the middle fossa and the glossopharyngeal and the vagus by a small filament in the jugular foramen. For our study we choose not to consider the cervical rootlets; however, they are unquestionably involved in these interneural anastomoses and external ear sense (Bischoff, 1865; Denny-Brown and Yanagisawa, 1973; Gray, 1980).

The cephalic territories of the trigeminal and glossopharyngeal nerves were clearly defined in rhizotomy series (Krause, 1896; Cushing, 1904, 1905; Dandy, 1927; Stookey, 1928; Hoover and Poppen, 1936). However, these cases indicated a sensory role within the deep ear for only the trigeminal nerve. During this same period it was suggested, on clinical grounds, that the facial nerve had a general somatic sensory component. It was noted, for example, that crude facial sensation remained after trigeminal ablation, which could be eliminated by facial nerve section (Cushing, 1904; Spiller, 1906; Souques and Hartmann, 1924). That this sensory function might be important in the ear was implied by the ear pain and subtle canal hypaesthesia occasionally encountered in Bell's palsy (Brodal, 1965, 1969).

Ramsay Hunt (1907) first called attention to the significance of the association of herpes zoster vesicles in the ear and facial palsy. He reasoned that the paralysis identified the nerve responsible for the eruption. Therefore, there had to be an aural sensory aspect to the facial nerve, the inference being that the geniculate ganglion served more than taste. Spillane (1954) found this reasoning to be tenuous. He pointed out that more than one nerve might be involved in herpes zoster and that Hunt had no autopsy proof substantiating his model. In a recent review of the Ramsay Hunt syndrome, or herpes oticus with facial palsy, it was noted that more than one nerve was always clinically affected (Heathfield and Mee, 1978). The few autopsy reports actually describing the geniculate ganglion in this syndrome did not substantiate a consistent or isolated ganglionitis (Sachs and House, 1956).

The aural afferent function of the facial nerve (as well as others) also found support in cranial nerve stimulation performed in the investigation of primary otalgia (Jefferson, 1931; Reichert, 1933; Furlow, 1942). Operative procedures in the posterior fossa on a handful of conscious patients allowed identification of the affected nerve by reproducing the patients' ear pain. The chorda tympani in patients with otalgia was shown to evoke ear pain if stimulated (Rosen, 1953), as did the greater superficial petrosal nerve (White and Sweet, 1969).

If facial general somatic afferents to the ear exist, they probably travel in the nervus intermedius, chordi tympani and greater superficial petrosal nerve, all known to carry afferent fibres (Foley and Du Bois, 1943). In addition, small filaments from the vertical facial nerve segment to the posterior ear canal have been described surgically (Hitselberger and House, 1966). Such innervation was supported by geniculate ganglion degeneration studies (De Gaetani, 1906–7). The majority of ganglion cells degenerated with chorda tympani sectioning; the remainder required sectioning of not only the greater superficial petrosal but also the facial nerve proper. The aural connection of geniculate cells was further corroborated by microelectrode recordings from the ganglion which indicated a mechanoreceptor, but not a pain system (Boudreau *et al.*, 1971).

Despite this indirect support of a facial nerve sensory component in the ear, actual anatomical evidence (such as that which exists for the trigeminal, glossopharyngeal and vagus nerves) was never found. Nevertheless, Brodal (1947) felt that the evidence from comparative neurology for a vestigial cutaneous afferent component was conclusive. He based this view primarily on findings in the human fetus (Larsell and Fenton, 1928; Pearson, 1945) and Rhinehart's (1918) albino mouse report.

The foregoing anatomical and clinical observations correlated well with histological demonstrations of fibres from the seventh, ninth and tenth cranial nerves in the descending trigeminal nucleus in the brainstem (Brodal, 1947; Kunc, 1960; Kerr, 1962). Assuming that all cranial somatic afferents join this nucleus, it remained only to determine the exact origin of these several nerves.

Cushing (1904, 1905) noted that the posterior line of the trigeminal sensory loss on the face crossed the pinna and was met by that produced by upper cervical rhizotomy. The residual sensation about the external ear was assumed to be vagal (Frohse, 1895; Krause. 1896). More than half a century later, Denny-Brown and Yanagisawa (1973) clarified this in a magnificent primate study. The 'remaining aesthesia' (Sherrington, 1898) between anaesthetic trigeminal and cervical zones could be enhanced by subictal strychnine treatment and then pared down sequentially first by glossopharyngeal-vagal section and then facial-acoustic nerve section.

Thus it was that sensory observations in animals and man, histological brainstem studies, clinical observations and anatomical dissections effected a reasonable consensus that the external ear including the tympanum was served by multiple nerves. Exactly how these cranial nerves related functionally in the deep ear and what was their degree of autonomous supply and/or overlap remained unclear, as evidenced by a contradictory interpretive literature. Graves and Edwards (1944) and Haymaker (1969) illustrated the canal and tympanum anteriorly as trigeminal and posteriorly as vagal (fig. 1). *Gray's Anatomy* (1980), however, describes the tympanum as not only trigeminal and vagal but also glossopharyngeal; territories are not mentioned. Testut and Latarjet's anatomy (1930) depicted the nervus intermedius as also supplying the tympanum *via* the auricular branch of the vagus. *Gray's Anatomy* (1980) states that the role of the nervus intermedius in the canal is an 'undetermined area' and does not consider its tympanic role. Cunningham (1964) described only the inner surface of the drum as glossopharyngeal, but Schadé (1966) denied this, feeling that it supplied not the tympanum but only the medial wall of the tympanic cavity. Krieg (1953) concurred with the ninth nerve's presence but felt it was entirely motor! Brodal (1969), commenting on the multinerve innervation, felt that a single nerve's 'deficiency' would scarcely be detectable. Truex and Carpenter (1969), ignoring the drum altogether, found a vagal innervation to the posterior wall of the external canal. Krieg (1953) alone credited no cranial nerve other than the trigeminal as having a measurable innervation to the deep ear, but he failed to describe any data.

Since extensive deep ear sensory mapping for the nontrigeminal nerves is minimal, this conflicting literature may have stemmed from inference based on the original trigeminal territories mapped by Davies (1907), Cushing (1904, 1905), and Krause (1896). If the premise of multiroot anatomy and discrete but limited fifth nerve findings, especially over the tympanum, is accepted, it was not unreasonable for some authors to have anticipated that the other nerves similarly had independent or at least joint areas of supply. It is our bias that these assumptions were further reinforced by a relatively small number of very carefully studied otalgia cases which may have confirmed multiroot innervation but did not clarify the question of territories. A thorough review of the otalgia literature was undertaken by White and Sweet (1969). Undoubtedly presumptions as to innervations were also rationalized, if the awkwardness of adequate deep ear examination without the aid of the operating microscope is considered.

Deep ear sensory mapping had its closest scrutiny by the pioneers of gasserian ganglionectomy (Krause, 1896; Cushing, 1904, 1905; Davies 1907). Their series stand in brilliant comparison with the relatively few and often incomplete case comments after facial, glossopharyngeal and vagal section. (This literature is summarized in Tables 8–10.) Possibly due to the paucity of aural findings, no report dealing principally with the deep ear sensory findings of these latter nerves exists. Cushing (1904, 1905) mapped the ear as well as the head in detail in 26 cases where patients had trigeminal ganglionectomy or root section. All but one patient had generalized anaesthesia of the tympanum; he experienced only anterior anaesthesia. The canal changes were not as consistent, but the anterior aspect was most commonly affected. Davies' (1907) similar study of Horsley's cases was even more detailed than Cushing's. He found anaesthesia of part or all of the tympanum in 14 of 24 cases, and 21 of 25 canals were at least partly affected. A lack of correlation between the degree of facial sensory loss and deep ear findings was also noted.

In our series, we found this lack of correlation to be true only with the glycerol and neurovascular decompression groups who had only minor if any facial hypaesthesia. With any substantial sensory loss, however localized, the tympanum was consistently anaesthetic in our series. The clinically affected divisions by examination of facial sensation did not necessarily correlate with ear findings. For example, the patient with trigeminal neurinoma (Case 1, Table 7) had only a patch of maxillary hypaesthesia but had major canal and tympanum anaesthesia. A patient treated by glycerol injection (Case 3, Table 3) had division I and II findings without any division III disturbance, but the ear anaesthesia was definite. These observations are perhaps significant, realizing the anatomical identification of the auriculotemporal nerve supply to the ear with the third trigeminal division.

In 6 cases, Krause (1896) had corroborated the anterior canal predilection for findings after gasserian ganglionectomy. He concluded, however, that the tympanum was entirely vagal, in agreement with one anatomist, Frohse (1895). Wolff (1963), in a peculiarly inexact description, noted normal canal and tympanic membrane sensation in 22 patients, *some* with complete section of the trigeminal sensory root, and some who were normal volunteers! Of the 14 trigeminal cases with solitary or multiple nerve deficits that we studied, 10 had tympanum signs, and all had some degree of canal findings. Of the 10 with any tympanum sensory change, all but one had anaesthesia. This absolute finding prevailed for no other nerve (*see* figs. 2, 3).

Very few reports of ear examinations in seventh nerve dysfunction exist (*see* Table 9). The classic otalgia case of Furlow (1942) had tympanic hypaesthesia on a single early examination. White and Sweet (1969) described 'normalgesia to hypalgesia' of the deep ear in 3 patients with nervus intermedius section. Only 2 of an additional 14 patients with nervus intermedius section had sensory notations (Clark and Taylor, 1909; Okonek, 1951; White and Sweet, 1955; Sachs, 1968). Sachs (1968) reported the largest single series (9 cases), but did not indicate sensory findings. We studied 8 patients with intermedius section or geniculate ganglionectomy, none of whom had sensory findings. These negative findings may be due to overlap innervation of the posterior canal by seventh, ninth and tenth cranial nerves (Brodal, 1965), an inadequate rhizotomy, or timing of the examination. In regard to the latter, we did note transient canal hypaesthesia in several seventh nerve cases. If a deficit was to persist, it was present after two weeks. This nerve was the only one to manifest transient signs.

Although incomplete nervus intermedius rhizotomy is a possibility for our findings, against this criticism is the consistently depressed postoperative lachrimation and the fact that all cases had at least two fascicles cut without facial, hearing or vestibular deficits. The usual number of nerve rootlets found in a large series of human dissections is two (Rhoton *et al.*, 1968). Sachs (1968) cautioned that the intermedius may run substantially in the vestibular nerve. Geniculate ganglionectomy should address the question of denervation adequacy (Saito *et al.*, 1970; Pulec, 1976); however, in 3 of our unrevealing cases this procedure was indeed done. If the explanation for negative deep ear findings after intermedius section is due to common skin innervation by the seventh, ninth and tenth cranial nerves (Brodal, 1965), the normal examinations in Cases 1–4 (Table 5) after sectioning of these nerves together, tend to refute this reasoning.

The posterior external canal has been described as consistently hypaesthetic to pin prick or light touch of a cotton wisp in acoustic neurinoma, whatever size, reputedly due to disturbance of the sensory component of the facial nerve (Hitselberger and House, 1966). This could not be confirmed by Eviator and Goodhill (1968). We noted this finding in 1 of the 3 neurinoma cases not involving the trigeminal nerve. Curiously, the sign was absent postoperatively in spite of a facial palsy (Case 10, Table 4). In the other 2 cases, both patients had canal hypaesthesia and 1 had a patch of anaesthesia *after* operation. A postoperative acoustic neurinoma series for sensory findings and correlations with preoperative signs has not been reported.

Diligent sensory examinations of the ninth nerve territories were recorded by Dandy (1927) and Stookey (1928). Although not stated as such, it is reasonable to assume these careful examinations did indeed include the deep ear and presumably yielded nothing. However, Haymaker (1969) erroneously stated that Dandy *reported* no sensory loss over the tympanum. Dandy simply did not record any tympanic examination. Davies (1907), in describing trigeminal territories, noted a unique patient who lacked a tympanic membrane due to old sepsis. The greater part of the external canal was anaesthetic from the trigeminal ablation; however, 'beyond the site of the membrane, horse hair stimulation produced a feeling of light touch'. Possibly this represented the ninth nerve innervation of the tympanic cavity, but it could be facial, vagal or all three. This is the only direct examination of the middle ear reported. However, Erickson (1936) recorded the effect of eustachian tube insufflation after ninth nerve section as being no longer painful in comparison with the opposite side. Without tympanic sensory notation he also noted the loss of cough reflex with tympanum stimulation. Whatever the deficit, in our experience the cough reflex was unpredictable. We presume that the sensation contribution of the ninth nerve is essentially exclusive of the external ear; despite rhizotomy case reports (Table 10), no case series actually describing an examination of the ear exists. We did not examine the ninth nerve in isolation, but even when taken with the facial or vagus nerve, no sensory findings ensued.

Since the vagus nerve may contribute to the syndrome known as glossopharyngeal neuralgia (Dandy, 1927; Fay, 1927; Peet, 1935; Karnosh *et al.*, 1947), in this syndrome we routinely section all of the ninth nerve and the upper roots of the vagus. We have no patients with isolated vagal section and have found no sensory examinations in the subject review. Since pain confined to the ear has been reported in glossopharyngeal neuralgia (Rushton *et al.*, 1981), it was important to scrutinize the joint supply to the ear of the ninth and tenth nerves.

The largest series of ear examinations after vagoglossopharyngeal rhizotomy included 6 cases (White and Sweet, 1969). One patient had minimal tympanum hypalgesia, and 4 had canal findings. Like our cases, these were complete glossopharyngeal sections with partial vagal section. Our Case 1 (Table 6), after failure of incomplete vagal section, had total vagal and glossopharyngeal nerve section for throat pain. One patient (Case 6, Table 6), after successful surgery for hemifacial spasm, suffered unilateral palatal paralysis, hoarseness and profound swallowing difficulty for four months. Unilateral anaesthesia of the affected oropharynx persisted. We were perplexed by this complication because the seventh and eighth nerves were undisturbed, but a total ninth and tenth paralysis existed for some time. Case 4 (Table 6) had unilateral deafness, hoarseness and swallowing difficulty associated with palatal paralysis and ipsilateral pharyngeal hypaesthesia. Case 5 (Table 6) was similarly affected by a glossopharyngeal neurinoma. These 4 cases are critical to understanding the vagal nerve in relation to deep ear sensation. They represent total or near total vagal (as well as glossopharyngeal) loss, and yet neither they nor the other 2 patients with incomplete vagoglossopharyngeal sections had sensory findings.

When the vagoglossopharyngeal cases are added to the facial vagoglossopharyngeal group of 10 cases, only 1 demonstrated any changes, and these were in the anterior not posterior canal (Case 1, Table 5). At the very least, it would seem that there is no clinical basis for the reputed vagal dominance to the posterior tympanum and canal (Frohse, 1895; Krause, 1896; Haymaker, 1969).

Unfortunately, our knowledge of deep ear sensation exclusive of the trigeminal nerve is based almost entirely on the otalgia experience. If, as Boudreau *et al.* (1971) speculated, deranged neural traffic or an aberrant anatomy account for the ear pain, sensory mapping in that particular patient might be misleading. If the study of atypical material is a realistic concern, then the rarity of primary otalgia becomes compelling. Extrapolating from a large hospital experience with trigeminal neuralgia (White and Sweet, 1969) and the clinical spectrum of glossopharyngeal neuralgia (Rushton *et al.*, 1981) otalgia is one thousand times rarer than trigeminal neuralgia. If otalgia simply occurs as a random affliction of the aural sensory nerves and is not a reflection of some unique feature of those nerves, then trigeminal *otalgia* should be at least an entity. Despite its sensory dominance, we cannot find a single case where the fifth nerve is conclusively responsible for primary otalgia. There are, indeed, a number of cases in which trigeminal ablation failed to relieve ear pain (Weisenburg, 1910; Jefferson, 1931; Wilson, 1950; Pulec, 1976).

In conclusion, only the trigeminal nerve of the four general somatic afferent cranial nerves to the ear retains an absolute area of sensory dominance. Focal or generalized anaesthesia of the tympanic membrane occurs only with trigeminal disturbance. Lack of this finding, however, is not necessarily indicative of an intact trigeminal nerve. Sensory findings within the canal are not indicative of any particular cranial nerve disturbance.

APPENDIX

TABLE 3 FIFTH NERVE CASE MATERIAL

				Sensory findings	
No /Age/Sex	*Problem*	*Treatment*	*Result of treatment*	*Deep canal*	*Tympanum*
1/66/M	Trigeminal neuralgia, divisions II, III	Subtotal section of sensory root	Pain free Diffuse facial hypalgesia	Normal 7 yrs postoperative	Anaesthesia
2/36/M	Trigeminal neuralgia Diffuse aching as well as lancinating pain, division II	(Inadvertent VIIth and VIIIth section in past) Total section of sensory root of Vth	Pain free Complete facial palsy Hypoglossal facial anastomosis Unilat deafness	Anaesthesia 13 yrs postoperative	Anaesthesia
3/73/F	Trigeminal neuralgia, divisions II, III	Glycerol injection	Pain free, div II anaesthesia Decreased corneal sensation	Focal anaesthesia 6 w postinjection	Focal anaesthesia
4/69/M	Trigeminal neuralgia, divisions II, III	Total section of sensory root in posterior fossa	Pain free Diffuse facial analgesia	Anaesthesia 5 yrs postoperative	Anaesthesia
5/69/M	Trigeminal neuralgia, divisions II, III Failed glycerol injection	Decompression of superior cerebellar arterial loop	Pain free No facial sensory loss	Hypaesthesia 6 w postoperative	Normal
6/54/M	Trigeminal neuralgia, division III	Subtotal section, sensory root	Pain free Analgesia of upper lip and tragus	Focal hypaesthesia 2 mo. postoperative	Normal
7/70/M	Trigeminal neuralgia, division III	Glycerol injections	Pain free Hypalgesia div I and II only Absent corneal	Hypaesthesia 6 w postinjection	Hypaesthesia
8/71/F	Trigeminal neuralgia, division II	Glycerol injection	Pain free Hypalgesia div. II only	Hypaesthesia 2 mo postinjection	Normal
9/71/M	Trigeminal neuralgia, divisions II, III	Glycerol injection	Facial hypalgesia div I > div III	Normal 2 mo postinjection	Normal
10/73/F	Trigeminal neuralgia, division III	Glycerol injection	No sensory deficit	Focal hypaesthesia 2 mo postinjection	Normal

TABLE 4. SEVENTH NERVE CASE MATERIAL

No /Age/Sex	Problem	Treatment	Result of treatment	Sensory findings	
				Deep canal	*Tympanum*
1/35/M	Otalgia deep, sharp lancinating pain, external canal trigger	Geniculate ganglionectomy and section of nervus intermedius	4 yrs postop, no pain Recent fluctuating hearing loss Rare pain episode 2½ yrs postop	Normal* 2 yrs postoperative	Normal
2/36/5	Otalgia: deep earache no triggers Rare similar symptoms in opposite ear Sjögren's syndrome	Nervus intermedius section	6 yrs postop 20% of preop pain	Normal* 4 yrs postoperative	Normal
3/15/F	Otalgia sharp, deep	Nervus intermedius section (1st operation)	Partial relief Then recurrence 18 mo postop.	Normal 8 mo. postoperative	Normal
4/28/F	Otalgia deep earache with occasional facial ache, sensitive external canal	Geniculate ganglionectomy	Fair. Decreased severity of pain	Generalized hypaesthesia 3 yrs postoperative	Normal
5/30/F	Otalgia deep sharp pain Possible Sjögren's syndrome	Geniculate ganglionectomy and nervus intermedius section	Dry eye problem postop for 6 mo Pain free for one year, then minor pain	Normal* 4 mo postoperative	Normal
6/38/M	Otalgia: deep, sharp pain	Nervus intermedius section (1st operation)	Recurrence postop after 1 mo.	Normal 2 yrs post surgery	Normal
7/55/M	Cluster headache syndrome	Nervus intermedius section	Pain free	Generalized hypaesthesia 3 yrs postoperative	Normal
8/60/M	Hemifacial spasm	Neurovascular decompression	Relief Facial palsy	Normal 2 w postoperative	Normal
9/55/F	Acoustic neurinoma 1 5 cm. Posterior canal hypaesthesia	Removal. No Vth or IXth involvement	Facial paresis	Normal 6 mo postoperative	Normal
10/30/F	Hemifacial spasm Equivocal diffuse canal and tympanum hypaesthesia	Removal of 6 mm acoustic neurinoma	Transient facial paresis	Focal anaesthesia Diffuse hypaesthesia 6 mo postoperative	Normal
11/34/M	Otalgia deep, sharp pain	Section of 2 slips of nervus intermedius (1st operation)	Relief for 1 mo Dry eye	Normal 1½ yrs postoperative	Normal

* Transient hypaesthesia

TABLE 5 FACIAL VAGOGLOSSOPHARYNGEAL CASE MATERIAL

No /Age/Sex	Problem	Treatment	Result of treatment	Sensory findings	
				Deep canal	*Tympanum*
1/58/M	Otalgia deep lancinating, normal ear	Section of 2 slips N intermedius, glossopharyngeal and 2 upper fascicles of vagus	Total relief. Ipsilateral pharyngeal hypaesthesia	Focal hypaesthesia 6 mo postoperative	Normal
2/17/F	Otalgia. Case 3, Table 2 Further op	(Intermedius failure) Section of glossopharyngeal and 2 upper fascicles of vagus	Failure Ipsilateral pharyngeal hypaesthesia	Normal 2 mo postoperative	Normal
3/40/M	Otalgia Case 6, Table 2 Further op	(Intermedius failure) Section of glossopharyngeal and 2 upper fascicles of vagus	Total relief Ipsilateral pharyngeal hypaesthesia	Normal 6 mo postoperative	Normal
4/35/M	Otalgia Case 12, Table 2. Further op	(Intermedius failure.) Section of glossopharyngeal and 2 upper fascicles of vagus	Total relief Ipsilateral pharyngeal hypaesthesia	Normal 3 mo postoperative	Normal

TABLE 6 VAGOGLOSSOPHARYNGEAL CASE MATERIAL

				Sensory findings	
No./Age/Sex	*Problem*	*Treatment*	*Result of treatment*	*Deep canal*	*Tympanum*
1/70/F	Lancinating throat pain with rare facial spread	Glossopharyngeal and total vagal section	Pain free Swallowing complaints with frequent choking	Normal 2 yrs postoperative	Normal
2/49/F	Lancinating throat pain radiating to deep ear	Glossopharyngeal and upper vagal section	Pain free	Normal 1 yr postoperative	Normal
3/71/F	Deep sharp ear pain radiating to throat Relieved by pontocaine spray to throat	Glossopharyngeal and upper vagal section	Pain free	Normal 6 mo. postoperative	Normal
4/64/M	Unilat. deafness Swallowing dysfunction Jugular foramen mass	Exploration and biopsy of hamartoma	No change	Normal 2 yrs postoperative	Normal
5/55/F	Headache, ataxia, unilateral paralysis of tongue, palate and vocal cord	Subtotal removal of glossopharyngeal neurinoma. Facial and trigeminal nerves not affected	Improved, headache and ataxia	Normal 3 mo postoperative	Normal
6/27/F	Hemifacial spasm	Neurovascular decompression (venous)	Relief No facial or acoustic deficit *Complication*: unilateral paralysis of palate and vocal cord. Anaesthesia of pharynx	Normal 6 wks postoperative	Normal

TABLE 7 NEURINOMAS AFFECTING MORE THAN ONE NERVE

				Sensory findings	
No /Age/Sex	*Problem*	*Treatment*	*Result of treatment*	*Deep canal*	*Tympanum*
1/36/F	Midfacial paraesthesiae from large trigeminal neurinoma displacing facial nerve	Total removal	Midface paraesthesiae. Facial nerve normal Tearing normal	Hypaesthesia 1 yr postoperative	Anaesthesia 'Focal hypaesthesia
2/65/F	Facial sensory findings Large acoustic neurinoma	Total removal, facial nerve not spared	Facial numbness, easy choking Slightly hoarse. Facial-hypoglossal anastomosis	Hypaesthesia 1 yr postoperative	Anaesthesia
3/66/F	Large acoustic neurinoma. Ataxic Vth, VIIth, VIIIth, IXth, Xth cranial nerve signs	Subtotal removal benign course, facial nerve not spared	Patchy facial sensory loss, div. I–div. III. Tonsil hypaesthesia. Hoarse	Anaesthesia 2 yrs postoperative	Anaesthesia
4/68/M	Large acoustic neurinoma. Deaf ear. Ataxic. Corneal sensation intact Anaesthesia of tympanum only	Total removal, facial nerve spared Vth, IXth and Xth nerves displaced by tumour	Facial palsy, hypaesthesia of corner of mouth only. Hoarse	Posterior-superior hypaesthesia 3 mo postoperative	Normal

TABLE 8 TRIGEMINAL NERVE LITERATURE

		Sensory examination			
Author	*Experience*	*Canal*		*Tympanic membrane*	
Davies (1907) (Horsley's cases)	25 cases	4 normal		10 normal	
		11 focal anaesthesia		7 focal anaesthesia	
		10 generalized anaesthesia		7 generalized anaesthesia	
Cushing (1904, 1905)	26 cases	Anterior canal anaesthesia		1 partial	
				25 complete anaesthesia	
Krause (1896) (cited by Davies)	6 cases	Anterior canal anaesthesia		Normal ('vagal')	
Wolff (1963)	? No of cases	Normal		Normal	
Saunders and Weider (1985) (this paper)	9 cases	Normal	2	Normal	5
		Focal anaesthesia	1	Focal anaesthesia	1
		Hypaesthesia	3	Hypaesthesia	1
		Focal hypaesthesia	2	Anaesthesia	2
		Anaesthesia	1		

TABLE 9. NERVUS INTERMEDIUS LITERATURE

Author	*Experience*	*Sensory examination*	
		Canal	*Tympanic membrane*
Clark and Taylor (1909)	1 case	Decreased sensitivity	No report
Furlow (1942)	1 case	Normal (trigger eliminated)	Hypaesthesia
Rosen (1953)	2 cases	No report	No report
White, Sweet (1955)	1 case	Normal	No report
Sachs (1968)	9 cases	No report	No report
Okonek (1951)	1 case	Anaesthesia anterior wall	No report
White and Sweet (1969)	3 cases	'Normalgesia to hypalgesia'	
Saunders and Weider (1985) (this paper)	8 cases	Transient hypaesthesia 4 Hypersensitive 1 Normal 3	Normal

TABLE 10

Author	*Experience*	*Sensory examination*	
		Canal	*Tympanic membrane*
A GLOSSOPHARYNGEAL LITERATURE			
Dandy (1927)	Several cases	No report*	No report*
Stookey (1928)	Several cases	Normal	No report*
Erickson (1936)	1 case	Anaesthesia	Eustachian inflation painless
Reichert (1933)	1 case	Normal	No report
Lillie and Craig (1936)	1 case	No report	No report
Hoover and Poppen (1936)	Several cases	No report	No report
White and Sweet (1955)	1 case	Normal	No report*
B GLOSSOPHARYNGEAL AND PARTIAL VAGUS LITERATURE			
White and Sweet (1969)	6 cases	Analgesia 1 Hypalgesia 3 Normal 1 No report* 1	Analgesia 1 No report* 5
C. GLOSSOPHARYNGEAL AND COMPLETE VAGUS LITERATURE			
Saunders and Weider (1985) (this paper)	4 cases	Normal	Normal

* Sensory examination performed, but this area not mentioned

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(Received June 26, 1984. Revised October 2, 1984. Accepted October 9, 1984)

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SUBCORTICAL CHANGES IN THE REGIONAL UPTAKE OF [^{3}H]-2-DEOXYGLUCOSE IN THE BRAIN OF THE MONKEY DURING EXPERIMENTAL CHOREIFORM DYSKINESIA ELICITED BY INJECTION OF A GAMMA-AMINOBUTYRIC ACID ANTAGONIST INTO THE SUBTHALAMIC NUCLEUS

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SUMMARY

Hemichorea/hemiballismus was induced in monkeys by localized injections of a gamma-aminobutyric acid antagonist into the contralateral subthalamic nucleus. During active dyskinesia, [^{3}H]-2-deoxyglucose was administered and, subsequently, regional cerebral metabolic activity was examined by autoradiographic exposure of brain sections. The results indicate that during dyskinesia there was an overall decrease in local cerebral glucose utilization in a number of structures on the side of the brain contralateral to the abnormal movements (ipsilateral to the drug injection). These structures included the injected subthalamic nucleus, both medial and lateral segments of the globus pallidus, the substantia nigra, and the ventral anterior and ventral lateral nuclei of the thalamus. On the basis of evidence that changes in the energy requirement of neurons are due mainly to changes in synaptic activity, the autoradiographic findings are interpreted as indicating that during experimental hemichorea/hemiballismus there was an overall decrease in synaptic activity of subthalamopallidal, subthalamonigral and pallidothalamic pathways on the side of the brain contralateral to the dyskinesia. This interpretation is discussed in relation to current theories of the pathophysiology of choreiform dyskinesias.

INTRODUCTION

Disordered function of the basal ganglia and related structures, whether due to pathological processes or pharmacological manipulation, is commonly associated with abnormalities of movement (dyskinesias) and muscle tone. In man, certain conditions are characterized by poverty and slowness of movement, whereas in other conditions abnormal involuntary movements occur. Involuntary movements may develop as a result of acquired (e.g. athetosis in cerebral palsy), or inherited

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(e.g. Huntington's chorea) disease, or they may be drug-induced (e.g. acute and tardive dyskinesia).

The primary site(s) of pathological process or drug action provoking dyskinesia is not, in most instances, established unequivocally but may certainly be diverse and centre on, for example, the basal ganglia and cerebral cortex (athetosis and Huntington's chorea), the subthalamic nucleus (ballism) or the neostriatum (presumed for acute and tardive dyskinesias). In contrast to this diversity, theories as to the pathophysiological mechanisms by which dyskinesias are mediated tend to be unified (Martin, 1967; Cooper, 1969; Carpenter and Sutin, 1983). The globus pallidus is generally regarded as being of central importance. From the anatomical point of view, it is certainly in receipt of massive projections from structures, such as the neostriatum (Szabo, 1967, 1970) and subthalamic nucleus (Nauta and Cole, 1978; Carpenter *et al.*, 1981*b*), disordered function of which leads to dyskinesia. Furthermore, it is the site of origin of one of the main output pathways of the basal ganglia, namely the pallidothalamic projection (Nauta and Mehler, 1966; Kim *et al.*, 1976), through which dyskinesia must, presumably, be mediated.

The evidence implicating the globus pallidus and thalamus in the mediation of dyskinesia stems not only from knowledge of their anatomical connections but, more particularly, from the effects of lesions upon dyskinesia in man and animals. Thus, in man, lesions of the globus pallidus (particularly the medial segment), its efferent pathways to the thalamus, or of ventral thalamic nuclei themselves, have been employed therapeutically to ameliorate a variety of dyskinetic disturbances including chorea, ballism and athetosis (*see*, for example, Cooper, 1969). In animals the best available evidence comes from the extensive studies of Carpenter and collaborators on the pathways which mediate dyskinesia induced in the monkey by lesions of the subthalamic nucleus. These studies indicate that dyskinesia so elicited can be abolished or prevented by additional lesions of the medial pallidal segment, fasciculus lenticularis or thalamic fascisculus (Whittier and Mettler, 1949; Carpenter *et al.*, 1950). The data, from both man and monkey, have been interpreted as indicating that abnormal hyperkinesia of basal ganglia origin, probably of whatever kind, is due to removal of normal inhibitory influences upon the globus pallidus (Martin, 1967; Carpenter and Sutin, 1983). Thus dyskinesia has been considered, either explicitly or implicitly, to be a consequence of abnormal hyperactivity of globus pallidus neurons projecting to the thalamus, such overactivity being counteracted by pallidal and thalamic lesions.

The evidence outlined above implicating hyperactivity of pallidal neurons in the generation of dyskinesia, while supported by a large body of data, comes entirely from studies of an indirect nature such as the infliction of secondary lesions. With the introduction by Sokoloff *et al.* (1977) of the 2-deoxyglucose (2-DG) uptake technique, the opportunity has become available for studying the brain mechanisms in operation in experimental dyskinesia by a more dynamic method. In this technique the regional uptake of a radioactively labelled analogue of glucose (2-DG) is visualized autoradiographically. Differential isotopic labelling between regions indicates differences in metabolic activity and thus, by implication, of neuronal electrical activity.

Available primate models of human-like dyskinesia are few, probably the best known being 'choreoid hyperkinesia' or ballism provoked by destructive lesions of the contralateral subthalamic nucleus (Whittier and Mettler, 1949; Carpenter *et al.*, 1950). Because of the unity of theories of the mediation of dyskinesia, in which abnormal activity of the pallidum figures so prominently, it is probable that this model is of significance to our understanding not only of the rare condition of hemiballismus in man but also of basal ganglia-related dyskinesias in general. Recently, hemichorea and hemiballism have been produced in the monkey by injection of antagonists of the neurotransmitter gamma-aminobutyric acid (GABA) directly into the subthalamic nucleus through an indwelling cannula (Crossman *et al.*, 1980, 1981, 1984). The dyskinesia thus elicited is closely similar to that produced in the monkey by subthalamic lesions and, when severe, resembles ballism in man (Whittier, 1947; Crossman *et al.*, 1984). The aim of the present study was to combine this pharmacological technique for the production of hemichorea/hemiballismus with the 2-deoxyglucose uptake technique in order to visualize the abnormally discharging neural populations in experimental dyskinesia.

MATERIAL AND METHODS

Experiments were performed on 3 adult monkeys (*Macaca irus*) weighing approximately 3 kg. All surgical procedures were performed under general anaesthesia (ketamine hydrochloride, 15 mg/kg and xylazine, 3 mg/kg i.m., supplemented as necessary) taking aseptic precautions. Two of the monkeys received intracerebral cannulae for drug injection and the third animal served as an unoperated control.

Cannulation and Intracerebral Injections

Under general anaesthesia a stainless steel cannula guide was inserted into the brain under stereotaxic control and secured to the skull with self-tapping stainless steel screws and dental acrylic cement. The stereotaxic coordinates used for locating the cannula guide were modified from the atlas of Shantha *et al.* (1968) on the basis of stereotaxic ventriculography (Crossman *et al.*, 1984). The cannula guide consisted of a guide tube (0.46 mm o.d., 0.25 mm i.d.) attached to a base, the latter being located on the surface of the skull to serve as anchorage for the cement. The cannula guide was normally occupied by a blank which bore a stainless steel stylette (0.23 mm diameter) to maintain the patency of the guide tube. Under brief general anaesthesia the blank and stylette were replaced by a stainless steel needle (0.23 mm diameter) attached to a mechanically operated micropump which permitted subsequent intracerebral injections to be made in the conscious animal. The design and operation of the pump have been described in detail elsewhere (Needham *et al.*, 1983).

Administration of 2-deoxyglucose and Autoradiographic Technique

A single dose of 2–3 mCi/kg of [^{3}H]-2-deoxyglucose (2-deoxy-D-2, 6-[^{3}H] glucose, specific activity approximately 30 Ci/mmol, Amersham) was administered intravenously to the control and experimental animals. In the experimental monkeys, administration took place once the animals had developed unambiguous dyskinesia following injection of bicuculline into the subthalamic nucleus. Forty-five minutes after the injection of 2-DG the animals were killed by barbiturate overdose administered i.v. The brains were frozen *in situ* in isopentane at −50° C. The tissue was blocked stereotaxically and the brains exposed by careful drilling. Coronal sections 20 μm in thickness of whole brain were cut on a cryostat (Bright), collected on warm glass slides and left to dessicate in the cryostat chamber at −20° C for several hours. The slides were sealed in x-ray cassettes loaded with LKB Ultrofilm and exposed for approximately 25 days at −25° C. The films were then developed in Kodak D19 developer (5 min at 20° C), and the parent sections were stained with cresyl violet.

Optical densities of structures on the autoradiographs were measured using a fibre-optic densitometer (Morton *et al.*, 1982). The method involved back illuminating the autoradiographs and using a 1.0 mm diameter optic fibre to transport the transmitted light to a spectrophotometer (Perkin Elmer), the analog output of which was fed to a digital voltmeter. Transmission readings were then converted into relative optical densities. For each structure examined, readings were taken bilaterally from at least 6 different autoradiographs and these data were used to calculate the mean percentage side-to-side change in relative optical density which resulted from the bicuculline injection. The data from the unoperated control animal were treated in a similar manner in order to identify any side-to-side asymmetries in 2-DG uptake in the normal brain (Mitchell and Crossman, 1984).

RESULTS

In the two experimental animals (CYN 100 and CYN 101) unilateral limb dyskinesia was provoked by injection of 30 μg bicuculline methiodide in 2 μl saline into the contralateral subthalamic nucleus.

Nature of the Dyskinesia

The dyskinesia was qualitatively similar to that observed in previous studies following injection of GABA antagonists into the subthalamic nucleus and reported in detail elsewhere (Crossman *et al.*, 1980, 1981, 1984). In animal CYN 100, limb dyskinesia began 6 min after drug injection with occasional flailing movements of the arm and leg, the arm being more prominently affected. The severity of the dyskinesia progressively increased so that within 15 min of drug injection the upper limb was involved in virtually continuous choreiform activity which, when particularly severe, warranted the term hemiballismus. Involvement of the lower limb remained mild and intermittent. In addition to limb dyskinesia a mild torticollis to the side contralateral to the injection was present and occasional periods of ambulation in circles, similarly directed. 2-DG was administered 20 min after the onset of dyskinesia. The same pattern of limb dyskinesia, with a marked preponderance of upper limb involvement, continued until the animal was killed.

In animal CYN 101, limb dyskinesia commenced 15 min after bicuculline injection with occasional swinging, circumductive movements of either contralateral limb. Administration of 2-DG was made 42 min after drug injection, at which time typically choreiform movements of the upper and lower limb were present frequently but intermittently, with short quiescent, nondyskinetic periods intervening. The upper limb movements were consistently more gross than those of the lower limb, this pattern of dyskinesia continuing until the animal was killed. In addition to limb dyskinesia, mild intermittent torticollis was noted but there was no circling behaviour. The dyskinesia exhibited by CYN 101 was notably less severe and of a more intermittent nature than that seen in CYN 100.

The control animal (CYN 102) showed no abnormality of movement and either sat quietly or moved normally about its cage during the period following administration of 2-DG.

Verification of Injection Sites

Microscopic examination of brain sections confirmed that the provocative injection site in each experimental animal was located within the subthalamic nucleus contralateral to the limb dyskinesia. In both animals the injection site lay in the caudal third of the nucleus, that in CYN 100 being the more rostral. In CYN 101 the injection was made near the dorsal border of the nucleus whereas in CYN 100 it was more deeply placed. In both animals multiple injections had induced considerable gliosis at the site of injection within the subthalamic nucleus and along the course of the injection track.

Autoradiographic Findings

Autoradiographs of selected brain sections are presented in figs. 1–15. In these figures, regions of high uptake of labelled 2-DG appear dark.

In autoradiographs from the two dyskinetic animals considerable side-to-side asymmetries in 2-DG uptake were found in a number of subcortical structures (figs. 1–13, Table). Autoradiographs from the control animal showed no such asymmetries (figs. 14, 15, Table).

With respect to the relative uptake between the majority of subcortical structures, the uninjected sides of the brains of dyskinetic animals (i.e. the sides ipsilateral to the dyskinesia) corresponded closely with the control animal. It is, therefore, reasonable to propose that asymmetries seen in the dyskinetic animals arose due to abnormalities induced by drug injection on the side contralateral to the dyskinesia.

Subthalamus. The normal subthalamic nucleus, both in the control animal (fig. 15) and on the uninjected side of the experimental animals (figs. 5, 6, 12, 13), was characterized by a high level of 2-DG uptake when compared with other subcortical structures. The injected subthalamic nuclei, on the other hand, showed markedly reduced uptake in both experimental animals (figs. 5, 6, 12, 13). In animal CYN 100 the entire subthalamic nucleus on the injected side showed reduced uptake, except for a small area at the injection centre corresponding to the region of heavy gliosis (fig. 6). In CYN 101 (the animal with milder dyskinesia) there was a more localized change in the subthalamic nucleus. There was a region of profoundly decreased 2-DG uptake in the dorsal two-thirds of the caudal half of the injected nucleus (fig. 13). A thin ventral strip in the caudal half of the nucleus (adjacent to the substantia nigra), and the whole of the rostral half of the nucleus, were unaffected (figs. 12, 13).

In CYN 101, in addition to the change in the subthalamic nucleus, there was a marked increase in 2-DG uptake in the zona incerta overlying the injected nucleus (fig. 13). Such a change was not observed in either CYN 100 or the control animal.

Globus pallidus. The globus pallidus was the site of dramatic changes in 2-DG uptake in both dyskinetic animals. In each case a marked decrease in 2-DG uptake was found in the globus pallidus (GP) of the injected side, the extent of the change being greatest in the animal with the most severe dyskinesia. In this animal (CYN 100) virtually the entire globus pallidus, including both lateral and medial pallidal segments (GP_L and GP_M), showed decreased uptake on the injected side (figs. 1-6). The affected region included the rostral pole of GP_L and part of its infracommissural extension (fig. 1).

In CYN 101 the changes were of a more regional nature in both medial and lateral pallidal segments. In the rostral half of GP_M decreased uptake was restricted to a comma-shaped region in the ventrolateral part of the nucleus. More caudally this region encroached dorsally eventually to include virtually the whole of GP_M (figs. 11, 12). An essentially similar topographic pattern of changes was seen in GP_L. The rostral pole of GP_L was free of change, evidence of decreased 2-DG uptake first being detected at the level of the rostral extent of GP_M. This took the form of a patch of decreased uptake in the ventral half of GP_L. On passing more caudally the patch extended dorsally to include all but the dorsal quarter of GP_L (fig. 11). Caudal to the level of the mammillary bodies decreased uptake of 2-DG was noted in the whole of GP_L with the possible exception of its dorsal infracapsular tip. In contrast to these changes, no consistent asymmetry was detected in 2-DG uptake by the globus pallidus in the control animal (fig. 14).

The caudate nucleus and putamen were without unequivocal asymmetry in either CYN 101 or the control animal. In CYN 100 a patch of decreased uptake was noted

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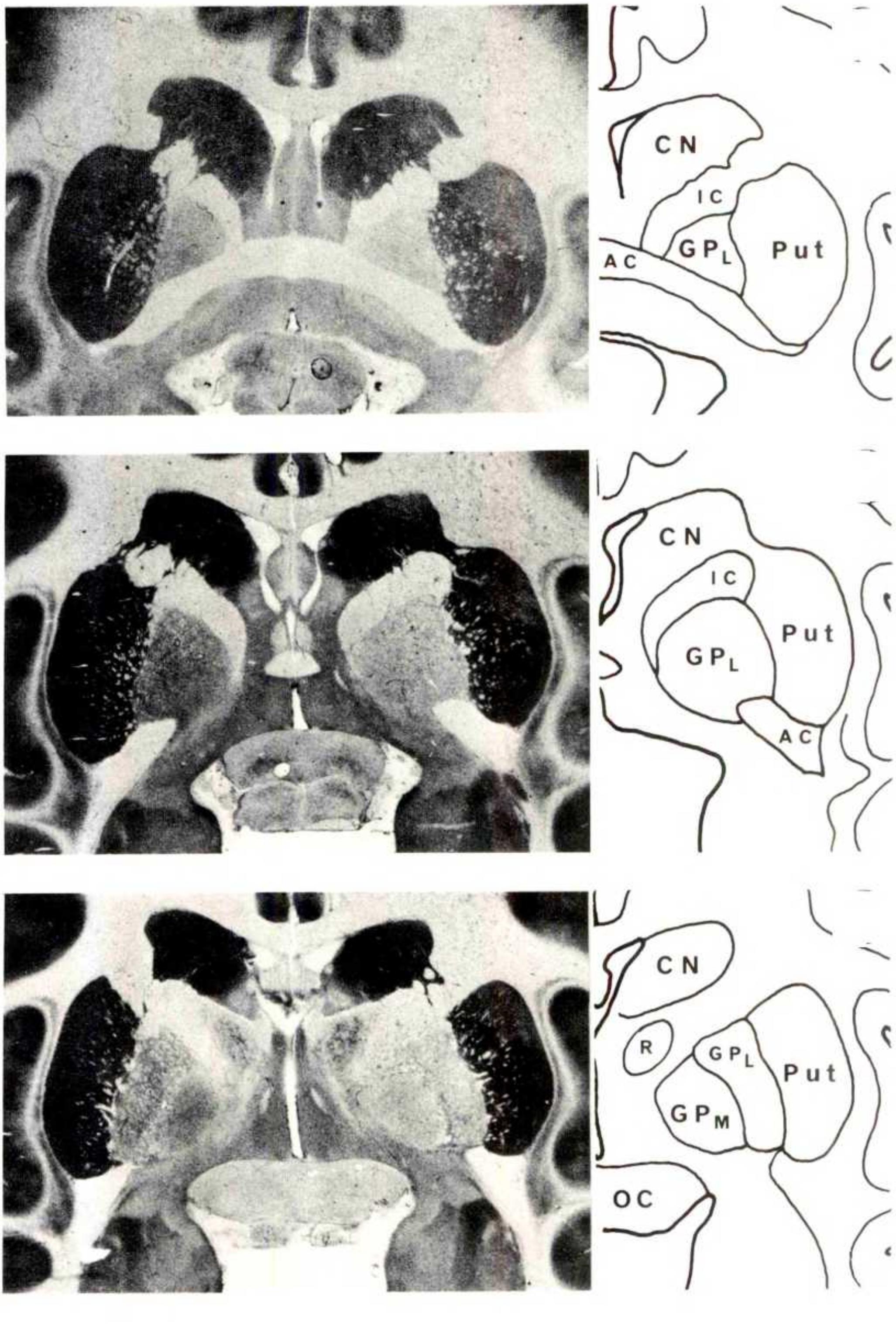
ABBREVIATIONS

AC = Anterior commissure
av = Anterior ventral nucleus
BC = Brachium conjunctivum
CM = Centromedian nucleus
CN = Caudate nucleus
CS = Superior colliculus
GP_L = Globus pallidus, lateral segment
GP_M = Globus pallidus, medial segment
Hb = Lateral habenular nucleus
IC = Internal capsule
LGN = Lateral geniculate nucleus
LP = Lateral posterior nucleus
m = Mammillary nuclei
MD = Mediodorsal nucleus
MG = Medial geniculate nucleus
npp = Nucleus tegmenti pedunculopontinus
OC = Optic chiasma
OT = Optic tract
PC = Posterior commissure
Pul = Pulvinar
Put = Putamen
R = Reticular nucleus of thalamus
rn = Red nucleus
SN = Substantia nigra
stn = Subthalamic nucleus
VA = Ventral anterior nucleus
VL_c = Ventral lateral nucleus, pars caudalis
VL_m = Ventral lateral nucleus, pars medialis
VL_o = Ventral lateral nucleus, pars oralis
VPL = Ventral posterolateral nucleus
VPM = Ventral posteromedial nucleus
ZI = Zona incerta
III = Oculomotor nucleus

FIGS. 1-15. Direct reversal prints of [^{3}H]-2-deoxyglucose autoradiographs from experimental animals (CYN 100: figs. 1-10, CYN 101: figs. 11-13) and control animal (CYN 102: figs. 14 and 15). Regions of greatest uptake of 2-DG appear darkest on the autoradiographs and regions of least uptake appear pale. Note that the subthalamic injection was made on the right side in CYN 100, but on the left in CYN 101. Increased uptake associated with intense gliosis around the injection track can be seen in figs. 5, 6, 7 and 13)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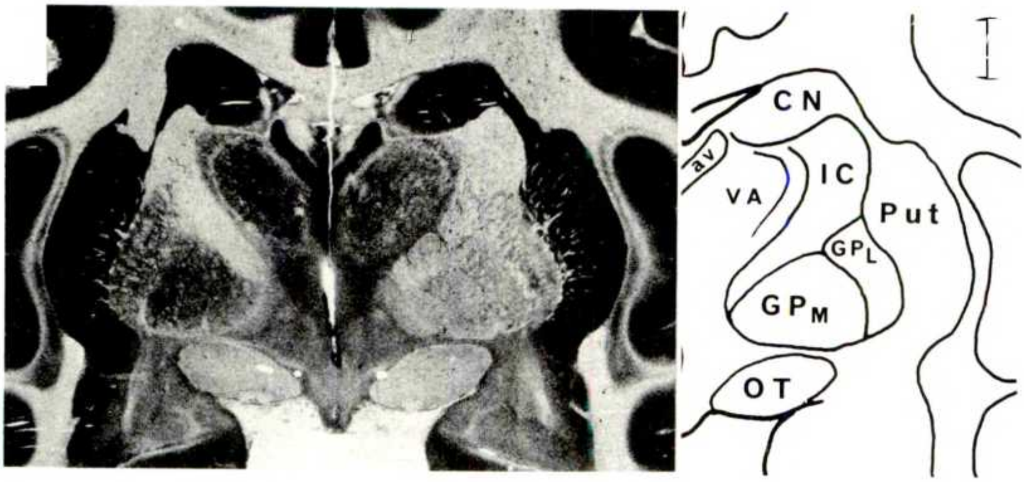
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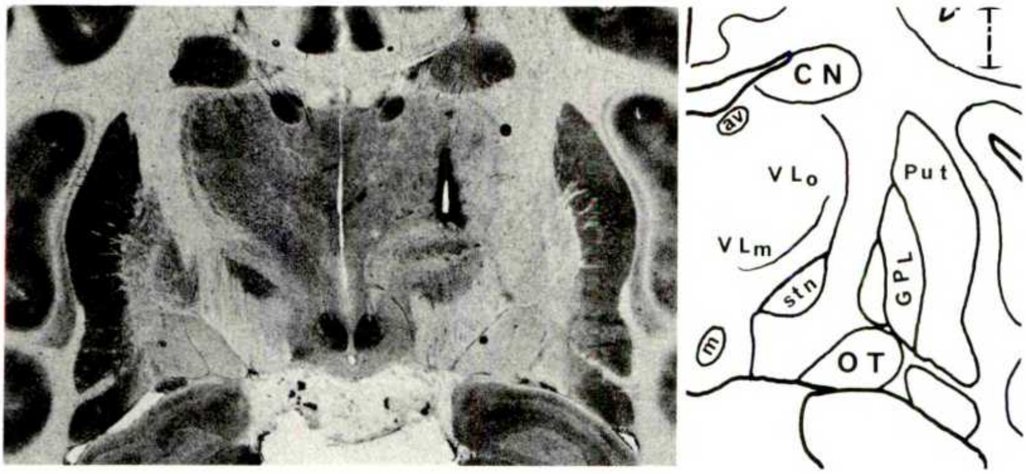
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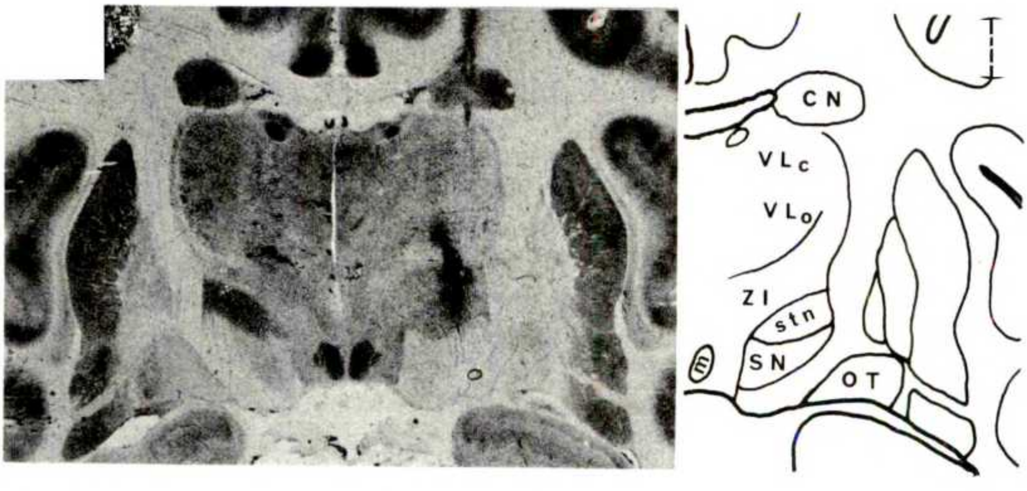
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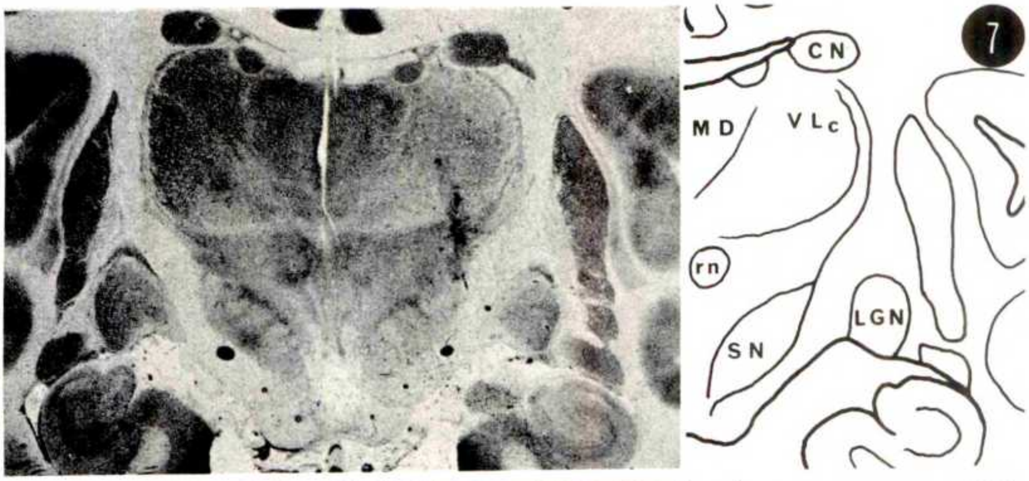
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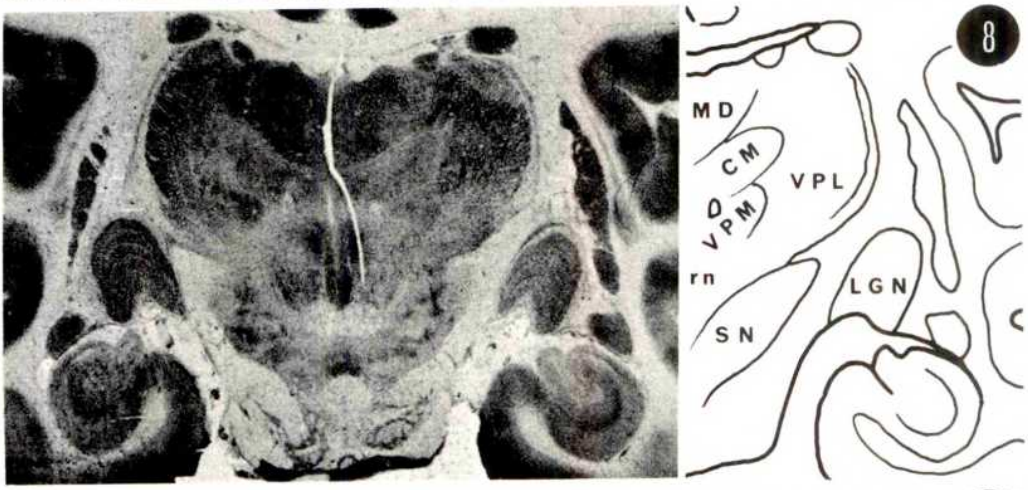
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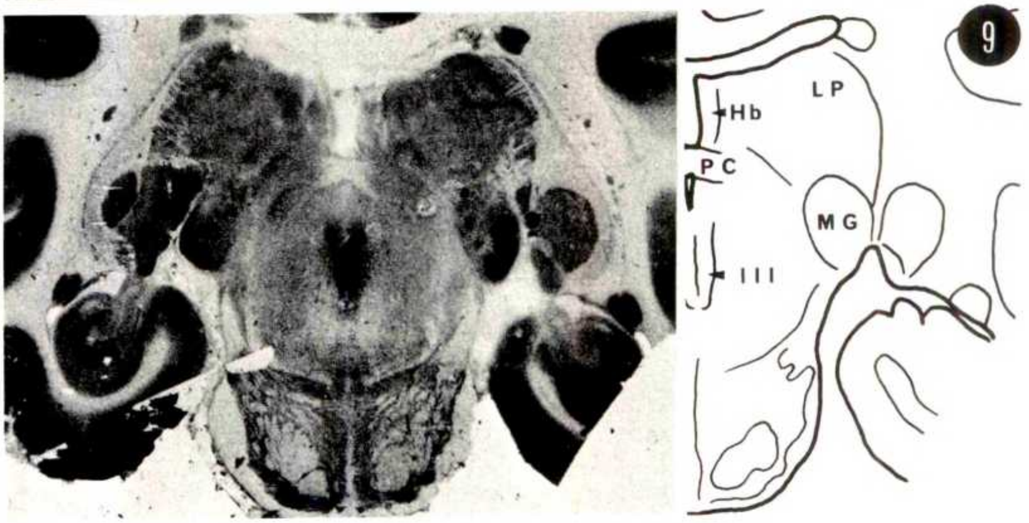
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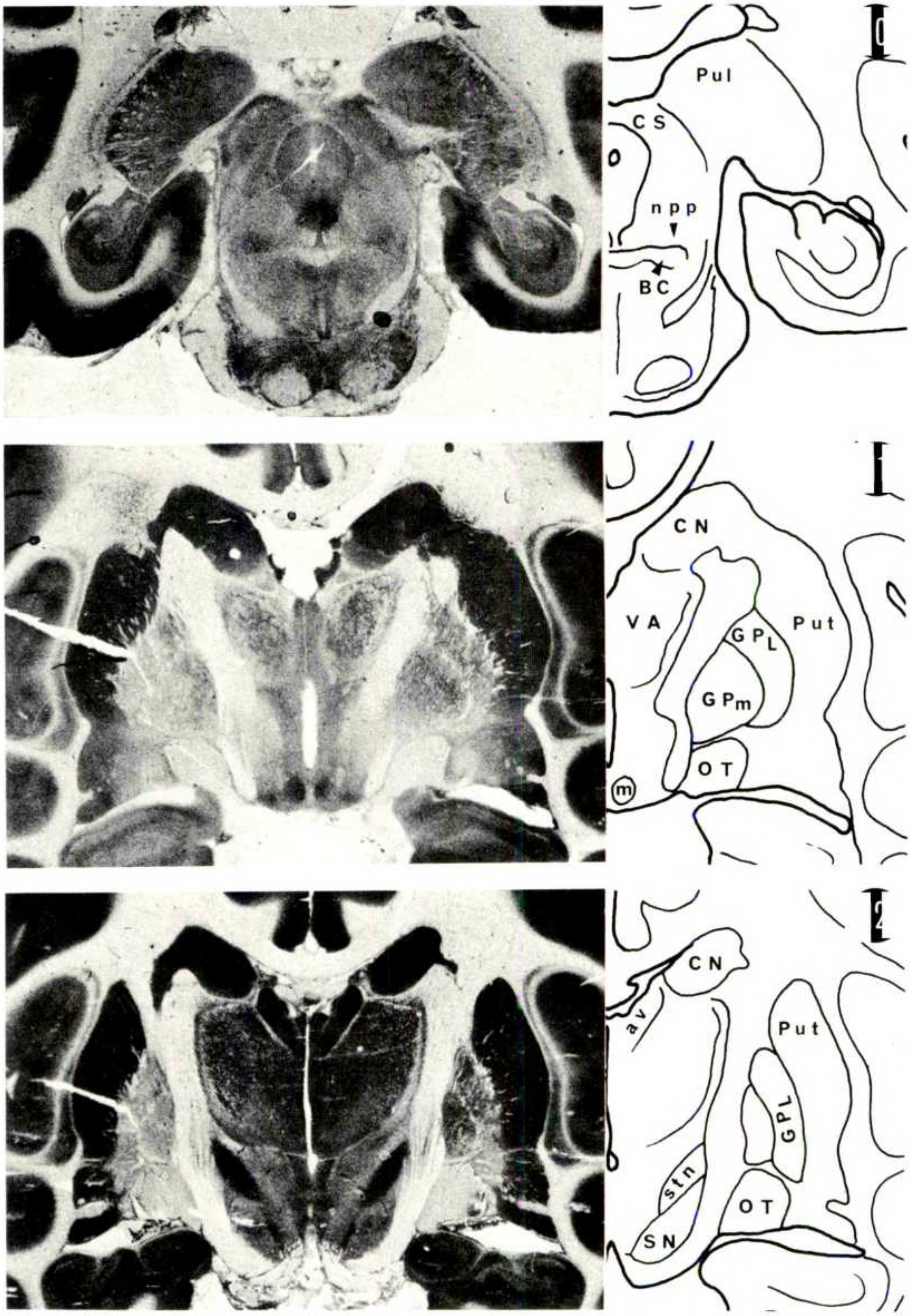
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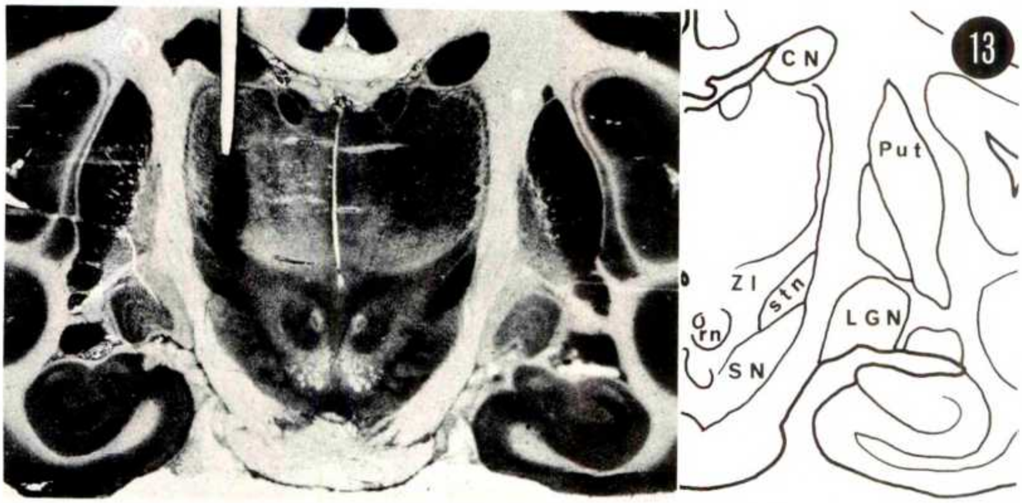

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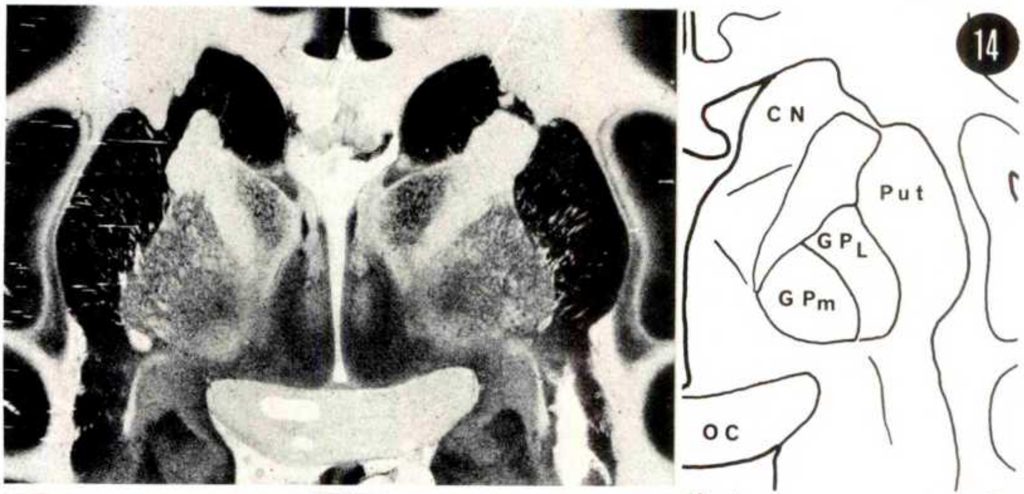

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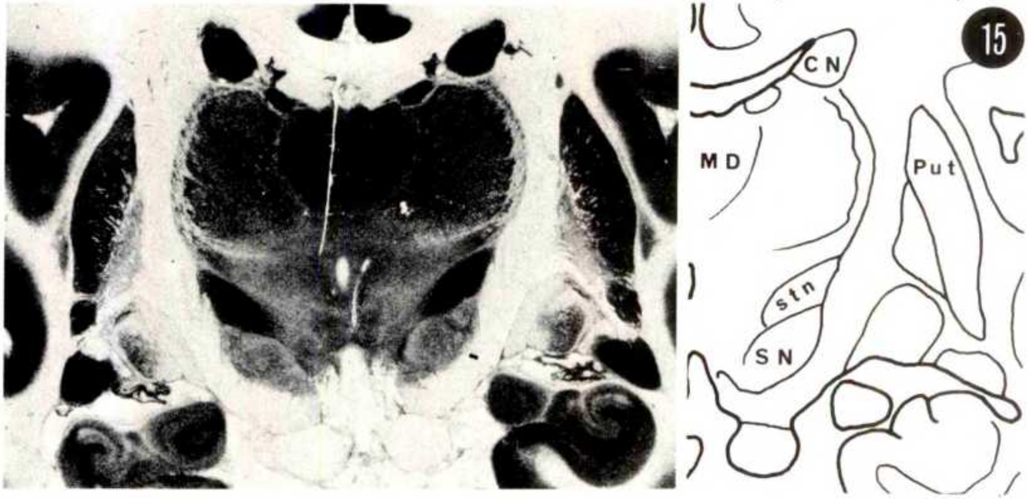

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TABLE. REGIONAL DENSITOMETRIC ANALYSIS OF [^{3}H]-2-DEOXYGLUCOSE AUTORADIOGRAPHS[1]

	CYN 100	*CYN 101*	*CYN 102*
Caudate nucleus	3.24 ± 0.40	1.18 ± 0.50	0.91 ± 0.36
Centromedian nucleus	10.3 ± 1.23	−2.8 ± 0.94	−1.35 ± 1.91
Dentate nucleus	2.48 ± 1.16	−1.08 ± 1.11	— —
Globus pallidus, lateral segment	20.4 ± 1.78	20.6 ± 3.5	−0.23 ± 0.09
Globus pallidus, medial segment	19.5 ± 3.57	11.5 ± 1.7	1.1 ± 1.29
Inferior colliculus	1.44 ± 1.49	−2.5 ± 1.07	1.9 ± 0.48
Inferior vestibular nucleus	0.8 ± 0.95	0 ± 1.12	−0.03 ± 1.91
Lateral vestibular nucleus	−0.2 ± 1.83	−0.07 ± 2.31	1.3 ± 0.65
Mediodorsal nucleus	2.48 ± 1.16	−1.08 ± 1.11	— —
Pulvinar	0.16 ± 1.25	0.5 ± 1.95	−1.72 ± 1.39
Putamen	7.0 ± 0.69	0.3 ± 0.5	0.59 ± 0.71
Red nucleus	7.77 ± 2.45	−2.1 ± 0.51	−0.56 ± 1.61
Substantia nigra	6.34 ± 2.72	2.46 ± 1.04	1.5 ± 2.15
Subthalamic nucleus	14.3 ± 1.3	12.0 ± 3.4	1.62 ± 1.02
Superior colliculus	2.93 ± 0.9	2.9 ± 1.57	0.5 ± 0.61
Ventral anterior nucleus	16.8 ± 4.9	4.18 ± 3.15	−0.81 ± 1.84
Ventral lateral nucleus pars caudalis	17.2 ± 4.0	3.2 ± 0.42	−0.83 ± 1.45
Ventral lateral nucleus pars medialis	13.0 ± 2.64	2.8 ± 0.96	1.5 ± 1.49
Ventral lateral nucleus pars oralis	16.84 ± 2.52	2.98 ± 1.24	1.3 ± 0.89
Ventral posterior nucleus	6.88 ± 2.83	0.45 ± 1.86	−0.08 ± 1.13
Zona incerta	−2.0 ± 2.83	−19.4 ± 11.85	1.9 ± 1.90

[1] The data are expressed in terms of percentage differences in relative optical density of the injected side compared with the control side for the experimental animals. Thus a positive number indicates that the injected side was paler than the uninjected side and a negative number indicates that the injected side was darker than the uninjected side. For the control animal, readings from the left and right sides of the brain were compared. The numbers are means and standard errors of readings taken from at least 6 autoradiographs which show typical changes in the nuclei or parts of nuclei as discussed in the text.

in the dorsal quarter of the putamen and adjacent caudate nucleus on the injected side (figs. 1–4).

Thalamus. A number of thalamic nuclei showed side-to-side asymmetries in the two dyskinetic animals, the most marked differences being found in CYN 100. In this animal, decreased uptake of 2-DG was found in the anterior ventral tier thalamic nuclei of the injected side. These included the ventral anterior nucleus (VA; fig. 4) and the ventral lateral nucleus (VL), pars oralis (VL$_{o}$), pars caudalis (VL$_{c}$) and pars medialis (VL$_{m}$; figs. 5–7). Asymmetry was also detected in the lateral habenular nucleus (fig. 9) and the centromedian nucleus (fig. 8), both of which showed less uptake on the injected side. Notwithstanding this asymmetry, the centromedian nucleus appeared considerably darker bilaterally than in the control animal. In addition to those nuclei with obvious basal ganglia connections, other nuclei in which asymmetry was found were the ventral posterior nuclear complex, particularly in its medial subdivision (VPM, fig. 8), and the ventrolateral part of the mediodorsal nucleus. Both these nuclei showed less uptake on the injected side. In CYN 101 thalamic asymmetries were much less clearly discernible than in CYN 100. Nevertheless, on the injected side, slight decreases in 2-DG uptake were found in parts of the ventral lateral complex and in the ventral posteromedial nucleus. Uniquely, the centromedian nucleus showed greater uptake on the injected side. No unequivocal asymmetry was found in other thalamic nuclei in the dyskinetic animals or in any thalamic nuclei in the control animal.

Substantia nigra. In CYN 100 the pars reticulata of the substantia nigra showed considerably less uptake on the injected than the uninjected side. This asymmetry was present throughout virtually the whole extent of the substantia nigra but was particularly evident in ventral parts adjacent to the crus cerebri (figs. 7, 8). Similarly, in CYN 101, asymmetry was observed in sections through the caudal part of the substantia nigra. No such asymmetry was found in the control animal.

Other brainstem nuclei. In CYN 100 only, substantially less uptake of 2-DG was found in the red nucleus on the injected side (figs. 7, 8) and, equivocally, in the rostral peribrachial part of nucleus tegmenti pedunculopontinus (fig. 10). In the medulla, some sections showed greater uptake in the cuneate and accessory cuneate nuclei of the injected side.

The foregoing description is restricted entirely to subcortical structures. Because of the vulnerability of LKB Ultrofilm to pressure-induced artefacts and the inherent heterogeneity of cortical 2-DG uptake, no attempt has been made to evaluate regional cortical asymmetries in this study.

A number of subcortical nuclei, apart from those explicitly mentioned in the text, were the subject of densitometric analysis but were not found to exhibit appreciable side-to-side asymmetry. These structures are indicated in the Table and may be identified in appropriate sections of figs. 1-15.

DISCUSSION

The histological verification of injection sites in the present study adds support to our previous finding, reported in detail elsewhere (Crossman *et al.*, 1984) that choreiform dyskinesia of the contralateral limbs can be elicited in the monkey by injection of GABA antagonists directly into the subthalamic nucleus. The application of 2-DG autoradiography revealed that, in association with dyskinesia, there were profound changes in the regional uptake of 2-DG in certain subcortical structures on the injected side of the brain. This is, to our knowledge, the first time that regional functional changes in the brain have been directly demonstrated in choreiform dyskinesia in the primate.

Interpretation of Changes in Regional 2-deoxyglucose Uptake

The interpretation of 2-DG autoradiography requires knowledge of the relative contribution of different cellular components to the overall pattern of 2-DG uptake. 2-DG is accumulated by the same membrane transport system as glucose, with which it competes as substrate for hexokinase, the first enzyme in oxidative metabolism (Sokoloff *et al.*, 1977). During periods of electrical activity the main increase in energy (glucose) requirement of neurons is for the maintenance of transmembrane ionic gradients, which are essential for the generation of action potentials and synaptic potentials. Thus the majority of the increase in energy consumption of activated neurons is associated with the ouabain-sensitive sodium pump (Mata *et al.*, 1980). The energy requirement for the maintenance of ionic gradients is greater for structures which have a high surface : volume ratio (such as axon terminals and dendrites) than for those with a low surface : volume ratio (such as neuronal perikarya, *see* Schwarz *et al.*, 1979; Mata *et al.*, 1980, for detailed presentation of evidence). The importance of this for the interpretation of 2-DG autoradiography was illustrated in an ingenious experiment by Schwarz *et al.* (1979) who examined 2-DG uptake in the hypothalamohypophysial system of the rat under conditions of characterized physiological stimulation. These workers demonstrated that increased firing activity in the pathway from the supraoptic and paraventricular nuclei to the posterior pituitary was associated with increased uptake of 2-DG in the posterior pituitary (i.e. the site of termination of the pathway) and not in the hypothalamic nuclei themselves (the location of parent cell bodies). Indeed, a lack of correlation between 2-DG uptake and single unit spike activity has recently been reported in the optic tectum of the reptilian brain (Auker *et al.*, 1983). It may reasonably be concluded that the overall level of 2-DG uptake by a brain region will predominantly depend on the density of synaptic arborizations and their level of activity. Most significantly, changes in 2-DG uptake, consequent upon some experimental or physiological manipulation, will reflect predominantly a change in the overall level of synaptic activity within the structure and not necessarily a change in the firing rate of the neuron cell bodies which it contains.

The synaptic architecture of any nuclear area is made up not only of the terminals of various afferent fibre populations but also those derived from local interneurons and axon collaterals of output neurons. Complex changes in all these components, beyond the spatial and temporal resolution of the 2-DG technique, may therefore summate to give a deceptively simple net increase or decrease in 2-DG uptake as revealed by autoradiography. Caution must thus be exercised in attributing changes in 2-DG uptake in a nucleus to alteration in, for example, a single afferent input unless there is justification from other evidence, such as a topographical organization of interconnections between structures. Just such justification appears in the present study for the interpretation of changes in 2-DG uptake in the globus pallidus and thalamus.

Regional Changes in 2-deoxyglucose Uptake During Dyskinesia

In both dyskinetic animals decreased uptake of 2-DG was found in the subthalamic nucleus, globus pallidus, substantia nigra and ventral thalamic nuclei of the injected side. Whatever the difficulties in interpretation of 2-DG autoradiographs, it is reasonable to conclude that changes in the neural activity in some or all of these nuclei are, therefore, implicated in the production of dyskinesia. As far as the subthalamic nucleus is concerned, uptake was decreased throughout the whole of the nucleus in one animal (CYN 100) whereas in the other (CYN 101) the region of decreased uptake was restricted to caudal and dorsal parts of the nucleus surrounding the injection site. This correlates well with the presence of less severe dyskinesia in CYN 101.

The dyskinesia induced by injection of bicuculline into the subthalamic nucleus is virtually indistinguishable from that produced by lesions of this nucleus (Whittier and Mettler, 1949; Carpenter *et al.*, 1950; Crossman *et al.*, 1984; M. B. Carpenter, personal communication). With lesions of the subthalamic nucleus it may be assumed that subthalamopallidal terminals in the pallidum are effectively underactive (or absent following wallerian degeneration). The most straightforward account of reduced uptake of 2-DG in the globus pallidus in the present study, therefore, is that it reflects hypoactivity of subthalamopallidal terminals in the globus pallidus. Other interpretations are possible but at present these would find little support from clinicopathological or experimental studies. That the change of 2-DG uptake in the globus pallidus was causally related to a change in subthalamic activity is supported by certain aspects of the known anatomical organization of subthalamopallidal relations which are illustrated in the present study. Thus although in the older literature the subthalamic projection to the pallidum was considered to terminate entirely in the medial pallidal segment, more recent autoradiographic findings have shown that subthalamopallidal fibres are distributed profusely to both pallidal segments (Nauta and Cole, 1978; Carpenter *et al.*, 1981*b*), including the rostral pole of GP_L around the anterior commissure. In the present study, profoundly decreased uptake of 2-DG was found in both pallidal segments. In the animal with most severe dyskinesia, the affected region extended to include the rostral pole of GP_L surrounding the anterior commissure. The animal with less severe dyskinesia showed more restricted changes in uptake both in the subthalamic nucleus and globus pallidus. Of considerable importance in establishing the functional relationship between these changes is the observation that they corresponded to the topographic organization of the subthalamopallidal pathway suggested by some anatomical studies. Thus on the basis of autoradiographic and retrograde tracing studies in the monkey, Carpenter *et al.* (1981*a*, *b*) have concluded that there is a direct rostrocaudal correspondence between the subthalamic nucleus and the globus pallidus, but that in the dorsoventral direction there is an inverse correspondence. This was precisely the finding in the present study where, in CYN 101, the caudal and dorsal part of the subthalamic nucleus showed reduced uptake in association with the caudal and ventral part of the globus pallidus.

The pars reticulata of the substantia nigra ipsilateral to the injected subthalamic nucleus showed decreased uptake of 2-DG. If our interpretation of changes in the globus pallidus is correct, then the decrease in the substantia nigra is not surprising. The subthalamic nucleus is known to project heavily upon the substantia nigra, probably particularly to the pars reticulata (Nauta and Cole, 1978; Carpenter *et al.*, 1981*b*). There is evidence, at least in subprimates, that the globus pallidus and substantia nigra are innervated by the same subthalamic nucleus neurons *via* axon collaterals (Deniau *et al.*, 1978; van der Kooy and Hattori, 1980). Thus decreased activity of subthalamic nucleus neurons would lead to depression of 2-DG uptake by corresponding terminals in both the pallidum and nigra.

Decreased uptake of 2-DG in the thalamus of dyskinetic animals was an unexpected finding and is more difficult to interpret. In support of a causal relationship between pallidal unit activity and thalamic uptake of 2-DG is the observation that the affected regions of the thalamus include nuclei with established connections from the pallidum, including VA, VL_o, VL_c, VL_m and CM (Nauta and Mehler, 1966; Kim *et al.*, 1976; DeVito and Anderson, 1982). If these changes are accepted at face value, they suggest decreased activity of pallidothalamic terminals and thus medial pallidal neurons during dyskinesia. However, such an interpretation does not conform with currently accepted theories of the pathophysiological mechanisms underlying dyskinesias nor with evidence from physiological studies on the subthalamopallidal pathway. A central feature of most pathophysiological theories of dyskinesias is abnormally increased pallidal activity. This is held to explain why dyskinesias are generally ameliorated by lesions of the pallidum or pallidal efferent pathways. Moreover, electrophysiological studies indicate that, at least in subprimates, the subthalamopallidal pathway is inhibitory upon pallidal neurons, probably releasing GABA as its neutransmitter (Larsen and Sutin, 1978; Perkins and Stone, 1980, 1981; Hammond *et al.*, 1983; Rouzaire-Dubois *et al.*, 1983). Decreased activity of this pathway would, therefore, be expected to lead to increased firing of pallidal neurons.

Reconciliation of these apparently conflicting lines of evidence would necessitate reformulation of the probable pathophysiological mechanisms mediating choreiform dyskinesia. The idea of global increases or decreases of neural activity in homogenous populations of pallidal or thalamic neurons as the fundamental factor in dyskinesia should probably give way to a more dynamic concept. It may be hypothesized that loss of regulatory input from the subthalamic nucleus results in demodulation of the activity of pallidothalamic projection neurons and that, under these circumstances, it is the precise temporal and spatial pattern of deranged pallidothalamic unit activity which is a major factor in the generation of abnormal movements. However, on average (for example, over a 45 min period as in the present experiments) the global activity of pallidothalamic neurons would be less than normal. Such a hypothesis permits interpretation of the 2-DG data at its face value and also acknowledges the considerable clinical and experimental evidence that pallidal neuronal activity sustains dyskinesia. This theory does not, however, easily reconcile with the electrophysiological evidence that the subthalamic nucleus normally exerts a powerful inhibitory effect on medial pallidal output neurons. It will be important for the further clarification of pathophysiological mechanisms in the basal ganglia to apply single unit recording techniques during dyskinesia and to test the generality of the present 2-DG findings in other forms of abnormal movement.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the expert technical assistance of Mr D. Peggs. This work was supported financially by the Medical Research Council.

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(*Received June 12, 1984. Revised October 18, 1984. Accepted October 23, 1984*)

Brain (1985), **108**, 423–438

SYMPATHETIC OUTFLOW IN MAN AFTER ANAESTHESIA OF THE GLOSSOPHARYNGEAL AND VAGUS NERVES

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SUMMARY

Bilateral lidocaine blocks of glossopharyngeal and vagus nerves in the neck were made in two healthy subjects to achieve deafferentation of arterial and cardiopulmonary baroreceptors. Microelectrode recordings of muscle nerve sympathetic activity (MSA) were made in one peroneal nerve; in one subject skin sympathetic activity (SSA) was recorded simultaneously in the other peroneal nerve. Following the nerve block in the neck there was a strong increase of MSA accompanied by temporary hypertension and tachycardia. The normal cardiac rhythmicity of MSA disappeared and the outflow appeared as bursts of impulses of variable duration occurring in a slow, irregular rhythm. Thus MSA became similar to SSA, but the activities never became synchronous. During the nerve block arousal stimuli evoked single bursts of MSA, a reflex response which normally occurs in SSA but not in MSA. It is concluded that (1) cardiac rhythmicity of MSA is due to baroreceptor influence; (2) a low level of MSA at rest depends on strong baroreceptor inhibition and not on a weak central drive; (3) central sympathetic outflows to skin and muscle are similar though not identical and the different characteristics normally observed are due to a large extent to different modulatory influences from afferent activity (presumably of baroreceptor origin) in glossopharyngeal and vagus nerves; and (4) baroreceptor deafferentation resulting in resting tachycardia and hypertension may explain sympathetic hyperactivity in the Guillain-Barré syndrome.

INTRODUCTION

Microneurographic recordings have shown that sympathetic impulses in peripheral postganglionic nerve fibres in man are discharged in different patterns in skin and muscle nerve branches. Muscle sympathetic activity (MSA) is involved in blood pressure homeostasis. It is composed of bursts of vasoconstrictor impulses synchronous with the pulse, the outflow of which is governed by inhibitory influences from arterial and cardiopulmonary baroreceptors. In each subject there is a close inverse correlation between spontaneous variations of blood pressure and variations in the strength of the sympathetic activity. On the other hand, there are large reproducible interindividual differences in the level of MSA at rest (expressed

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as sympathetic bursts/100 heart beats or bursts/min) and there is no significant correlation between a subject's level of MSA and his blood pressure level (Delius *et al.*, 1972*a*; Sundlöf and Wallin, 1977, 1978*a*).

Skin sympathetic activity (SSA) is composed of a mixture of sudomotor and vasoconstrictor impulses involved in thermoregulation. The impulses occur in bursts of variable duration and strength which are discharged in a fluctuating irregular pattern and there is no obvious cardiac rhythmicity and no obvious sign of baroreceptor influence. A typical feature of SSA, not seen in MSA, is that a strong sympathetic burst is evoked by an arousal stimulus or a deep breath. In addition, emotional reactions regularly cause a more long-lasting increase of SSA whereas there is little change or possibly some reduction in MSA (Delius *et al.*, 1972*b*, *c*; Hagbarth *et al.*, 1972; Bini *et al.*, 1980*a*).

It is well known from animal experiments that the phase lock between sympathetic neural discharges and the cardiac rhythm disappears after interruption of afferent inflow from arterial baroreceptors (Adrian *et al.*, 1932; Bronk *et al.*, 1936; Weidinger *et al.*, 1961; Downing and Siegel, 1963; Koizumi *et al.*, 1971; Taylor and Gebber, 1975; Barman and Gebber, 1980). Some observers (Bronk *et al.*, 1936; Alexander, 1945; Downing and Siegel, 1963; Koizumi *et al.*, 1971; Taylor and Gebber, 1975; Barman and Gebber, 1980) have reported a persisting rhythmic, although not cardiac-linked, discharge pattern after baroreceptor denervation, suggesting the existence of an intrinsic sympathetic rhythm, the frequency of which is similar to but not identical with the heart rate.

In man, transient elevation of blood pressure and heart rate have been observed following carotid endarterectomy (Angell-James and Lumley, 1974) and after surgical (Leriche *et al.*, 1935; Capps and de Takáts, 1938) and pharmacological (Mushin, 1945; Lampen *et al.*, 1949; Guz *et al.*, 1966) baroreceptor deafferentation. With sympathetic nerve recordings in man, an association between essential hypertension and changes in MSA has not been noted (Wallin and Sundlöf, 1979). However, in the rare cases of the Guillain-Barré syndrome with hypertension and tachycardia, there is an increase of MSA during the hypertensive period. It can be deduced that this clinical picture probably is due to a temporary partial damage to afferent baroreceptor pathways (Fagius and Wallin, 1983).

In the present study bilateral local anaesthetic blocks of the glossopharyngeal and vagus nerves in the neck were employed to produce transient baroreceptor deafferentation in man while recording sympathetic outflow to muscle and skin. The aims were (1) to study the character of MSA without baroreceptor modulation; (2) to detect possible differences in MSA after baroreceptor deafferentation between individuals with high and low levels of activity before the block; (3) to reveal possible common characteristics between MSA and SSA following interruption of the baroreceptor influence on MSA; and (4) to provide evidence for the postulate that transient hypertension and tachycardia in acute polyneuropathy (Guillain-Barré syndrome) may be due to involvement of baroreceptor afferents in the disease process.

SUBJECTS AND METHODS

The investigations were performed on two of the authors (J.F., male, aged 36 years, and G.S., male, aged 44 years), both healthy physicians with precise knowledge of the experimental design. Microelectrode recording of MSA was performed from the right peroneal nerve at the fibular head in one experiment (J.F.). In the second experiment (G.S.), MSA and SSA were recorded simultaneously from the left and right peroneal nerves, respectively, at similar positions in relation to the fibular head.

Nerve Electrodes and Display Systems

These were the same as in many previous studies (*see* Sundlöf and Wallin 1977). In short, an insulated tungsten microelectrode (diameter of uninsulated tip 1-5 μm) was inserted through the unanaesthetized skin into a suitable position in the underlying nerve. A similar electrode, but with larger uninsulated tip, was inserted subcutaneously 1-2 cm away and served as reference. The nerve signal was amplified in two steps (total gain × 50 000) and fed through a 700 to 2000 Hz bandpass filter for improving signal-to-noise ratio. An RC integrating network (time constant 0.1 s) was used to obtain a mean voltage display of the multiunit neural activity. Blood pressure was recorded either noninvasively every minute (subject J.F.) by an automatic blood pressure recorder (Dinamap, Criticon, Tampa, Florida, USA) or invasively (subject G.S.) through a catheter in the left radial artery connected to a pressure transducer EMT 35 and an electromanometer EMT 31 (Siemens-Elema, Stockholm, Sweden). The electrocardiogram (ECG) was recorded by surface chest electrodes and respiratory movements by a strain gauge attached to a rubber band strapped around the chest. Analogue signals of filtered and mean voltage neurograms, respiratory movements, intraarterial blood pressure and ECG were stored on tape (FM tape recorder Sangamo Sabre VI, Sangamo-Weston Schlumberger, Sarasota, FLA) for subsequent analysis. During the experiments corresponding signals were monitored on a storage oscilloscope and on an ink-jet recorder.

Blocking Technique

Atropine, 2 mg, was administered intravenously before the local anaesthesia. The aims were (1) to avoid the sudden combined effect of vagal inhibition and increased sympathetic outflow following local anaesthesia; and (2) to achieve mucosal dryness of the mouth and throat since swallowing was to be paralysed.

An injection of 4 ml of a 1 per cent lidocaine solution was made around the glossopharyngeal and vagus nerves at the base of the skull—pulsations of the needle from contact with the carotid artery served as an aid for localization. As the block was initially incomplete, the injection had to be made twice on the right side in subject J.F. Expected effects with inability to swallow, almost complete disappearance of phonation, inability to cough, bilateral Horner's syndrome (and increase of blood pressure and tachycardia, *see* Results) were seen in both subjects. Tongue paralysis (Mushin, 1945) did not occur in either subject. There were no subjectively detectable changes of respiration and the respiratory record remained essentially unchanged throughout the procedure.

Careful measures were undertaken to maintain free airways and provision had been made for managing a circulatory emergency. No harmful effects arose from the experiments; subject J.F. felt palpitations during the first few minutes following bilateral nerve block; in subject G.S. bilateral blocking was followed by a headache, lasting about 30 min longer than the transient hypertension, and an imperative need for micturition occurred.

General Procedure

The subjects lay comfortably, fully alert. The nerve recording electrode was inserted manually and adjusted until an appropriate nerve fascicle was encountered. The criteria for muscle nerve fascicles were (1) muscle twitches evoked by electrical stimuli delivered through the electrode and (2) afferent, mechanoreceptive activity evoked by stretching or tapping of the appropriate muscle but not by gentle skin touch. Corresponding guidelines for a skin nerve fascicle were (1) skin paraesthesiae without muscle twitches following electrical stimuli and (2) mechanoreceptive activity elicited by gentle skin touch within the fascicular receptive field. Further minute electrode adjustments were made until a multiunit sympathetic recording site was found. MSA and SSA were recognized and identified by their characteristic temporal patterns and responses to certain manoeuvres. Evidence for the sympathetic nature of the activities have been summarized previously (Vallbo *et al.*, 1979). In brief (1) the activity is efferent, as shown by injection of a local anaesthetic proximal and distal to the recording site; (2) the impulses are conducted with a velocity of approximately 1 $m \cdot s^{-1}$; (3) the activity is reversibly abolished by an intravenous infusion of the sympathetic ganglion-blocker trimethaphan; and (4) there is a clear relationship between changes of neural activity and succeeding sympathetic effector responses, such as sweating, changes of vascular resistance and blood pressure.

When a recording site was found with acceptable signal-to-noise ratio for sympathetic impulses, spontaneous activity was recorded during a 5 to 7 min rest. Then atropine was injected and nerve activity was recorded for another 5 to 7 min. Thereafter the local nerve blocks in the neck were performed. The interval between successful blocks on the two sides were 7 min in the first and 2 min in the second experiment.

In the first experiment the intrafascicular recording site remained unchanged during the whole procedure (140 min). In the second experiment the skin nerve recording site was unchanged whereas the electrode in the muscle nerve fascicle had to be adjusted slightly on two occasions following movement-induced impairment of the recording site. At the end of the experiments the positions of the electrodes having recorded MSA were tested again and found to have pure muscle nerve fascicle characteristics. During some phases of the recordings arousal stimuli were brought about by sudden noises, air puffs to the face, skin pinches or single electrical stimuli to the skin of the right arm.

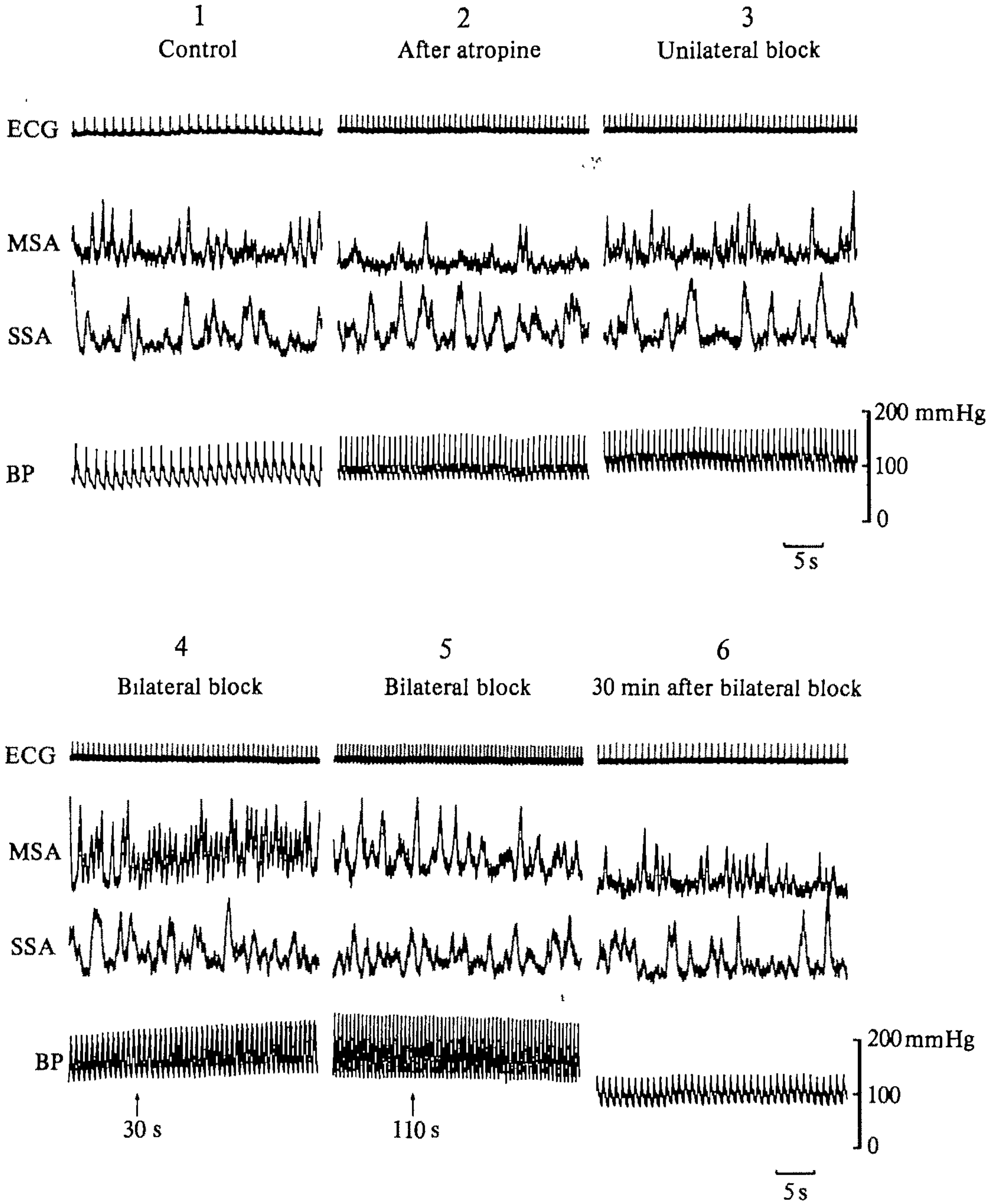
Analysis Procedure

Paper displays of mean voltage neurograms, ECG and respiratory movements were made by an ink-jet recorder (Mingograph 800, Siemens-Elema, Stockholm, Sweden) at two different paper speeds, 5 mm/s and 25 mm/s. From the 5 mm/s display, bursts of MSA were counted and expressed as bursts/100 heart beats and bursts/min. The 25 mm/s display was used for manual determination of sympathetic reflex latencies (Fagius and Wallin, 1980). For the inhibitory baroreflex, producing the pauses between the MSA bursts, the latency was measured from the R-wave of the ECG to the peak of the corresponding burst in the mean voltage neurogram, the peak being taken as the start of inhibition induced by the systolic pressure wave (for details of identification of corresponding burst, *see* Fagius and Wallin, 1980). Measured in this way the delay, which normally lies in the range of 1.2 to 1.5 s, includes both haemodynamic events and neural conduction time. For SSA reflexes the latency was measured from the arousal stimulus to the start of the evoked burst; nerve processing and conduction account for the normal range of 0.7 to 0.9 s (Fagius and Wallin, 1980). The mean latency was the average of 20 to 30 single determinations. For MSA bursts induced by arousal stimuli during the anaesthesia (*see* Results), latency was measured analogously to SSA reflex latency. In subject J.F., SSA reflex latency was determined from a separate recording some weeks after the nerve blocking experiment. The 25 mm/s paper display was also used for measuring the interval between peaks of SSA and MSA bursts, as described in the Results section.

Frequency power spectral analysis of 80 s samples of the mean voltage neurogram was performed by use of a waveform analyser (Data 6000, Data Precision, Danvers, Mass., USA). The same equipment was used for cross correlation between MSA and SSA mean voltage neurograms (subject G.S.) for selected 80 s samples from the tape.

RESULTS

Changes of blood pressure, heart rate and muscle sympathetic outflow are summarized in Table 1 and fig. 1. The level of MSA before the nerve blocks differed



1 Control

2 After atropine

3 Unilateral block

4 Bilateral block

5 Bilateral block

6 30 min after bilateral block

FIG. 1. Experimental records from subject G.S. Traces from above: electrocardiogram (ECG), muscle sympathetic activity (MSA) and skin sympathetic activity (SSA) (mean voltage neurograms) and intraarterial blood pressure (BP). Same timescale in all panels. Time notations in panels 4 and 5 indicate time after completed bilateral injection of anaesthetic.

considerably between the two subjects, but the main changes during the experimental procedure were essentially the same in both subjects. Atropine injection caused tachycardia, a slight increase of blood pressure and a marked decrease in MSA. Following unilateral nerve block in the neck, the level of sympathetic bursts/min became higher than in the control situation. After bilateral anaesthesia there was a dramatic increase of MSA and its cardiac rhythmicity was abolished. The increase was paralleled by tachycardia (maximum 155 beats/min in one experiment and 133 in the other) and marked blood pressure peaks (maximum 210/145 and 245/135, respectively).

TABLE 1 CHANGES OF BLOOD PRESSURE (BP), HEART RATE (HR) AND BURST INCIDENCE OF 'MSA' DURING THE EXPERIMENTS

Subject	*J F*				*G S*			
	BP	*HR*	*Bursts/100 heart beats*	*Bursts/min*	*BP*	*HR*	*Bursts/100 heart beats*	*Bursts/min*
Initial rest	120/70	68	20 4	14 0	120/60	50	57 0	28 5
After atropine	135/80	117	< 1	< 1	130/65	95	19 6	18 7
After unilateral block of ninth and tenth nerves	160/105	128	14 7	18 8	150/80	94	56 0	52 6
After bilateral block of ninth and tenth nerves	Max 160/145	Max 155	'Maximal' activity without pulse synchrony within 12 s		Max 245/135	First min 106 Thereafter Max 133	86 'Maximal' activity without pulse synchrony	91

In subject J.F. a 'maximal' sympathetic activity with widened bursts, completely lacking cardiac rhythmicity, occurred within 12 s after bilateral nerve block. In subject G.S. pulse synchrony of MSA was preserved during the first minute after bilateral nerve block (fig. 1, fourth panel); during this period a burst occurred corresponding to virtually every heart beat. The same pattern as seen in subject J.F. then followed, that is, long duration bursts without cardiac rhythmicity, strikingly similar to those seen in SSA (fig. 1, fifth panel). As illustrated in fig. 2 the maximal activity was similar in the two subjects, irrespective of the difference in burst incidence before the anaesthesia. Some elevation of the baseline of the mean voltage neurogram was seen in both subjects during this phase (*see* fig. 1, fourth and fifth panels). This type of activity lasted about 1 min in subject J.F. and about 5 min in subject G.S.; intervals between bursts then became successively longer. Long duration bursts were seen for 20 to 30 min, but cardiac rhythmicity began to recur 15 to 20 min after bilateral nerve block. After 60 min (J.F.) and 30 min (G.S.) the resting activity had regained normal appearance (fig. 1, sixth panel).

SSA was recorded only in subject G.S. The level of activity was high with frequent strong irregular bursts of impulses. Inspection of the record revealed no clear change during the whole experiment.

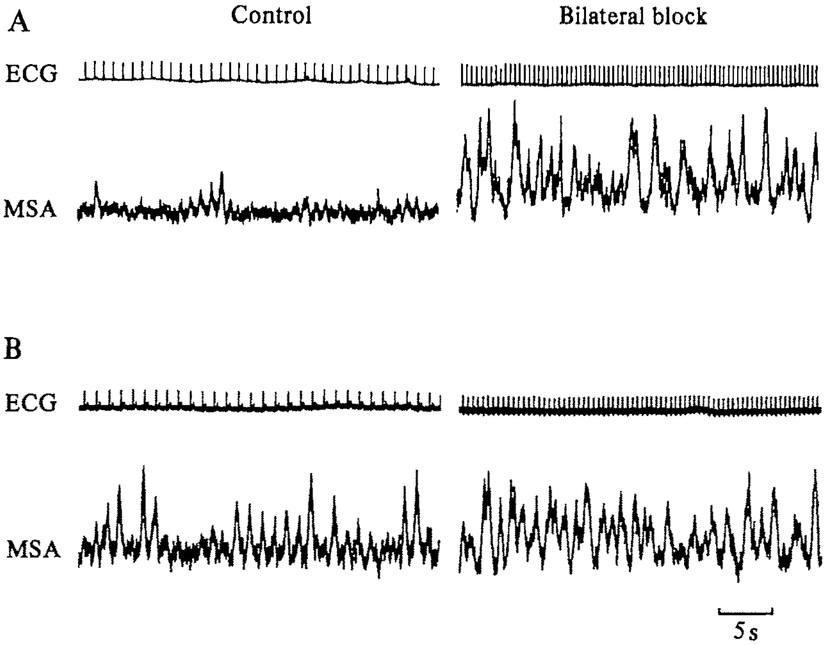


FIG. 2. ECG and MSA (mean voltage neurogram) in control situation and during 'maximal' activity following bilateral block of glossopharyngeal and vagus nerves. A, subject J.F.; B, subject G.S. Same timescale in all panels Note difference in level of MSA between subjects in the control situation and similarity following nerve block.

Manoeuvres Affecting MSA

In subject J.F. following bilateral nerve block, arousal stimuli regularly elicited distinct single bursts of high mean voltage amplitude (fig. 3, right), similar to the reflex bursts normally seen only in SSA. With the return of cardiac rhythmicity of MSA, the arousal responses became successively weaker and about 40 min after the bilateral nerve block they could no longer be evoked. In subject G.S. similar evoked responses occurred both in the SSA and MSA recordings during bilateral nerve block (fig. 3, left), although responses in the muscle fascicle were more difficult to evoke in this subject.

Reflex latencies are summarized in Table 2. The different latencies showed similar interrelationships in both subjects (the constantly longer latencies in subject J.F. reflect longer legs). During bilateral anaesthesia of the vagus and glossopharyngeal nerves, the latency from arousal stimulus to the onset of the evoked burst of activity was around 0.35 s longer in MSA than in SSA in the two subjects (fig. 3, left; Table 2). (In J.F. the SSA latency was determined in a separate recording at the same level in the peroneal nerve; this was considered justified since in subject G.S. SSA

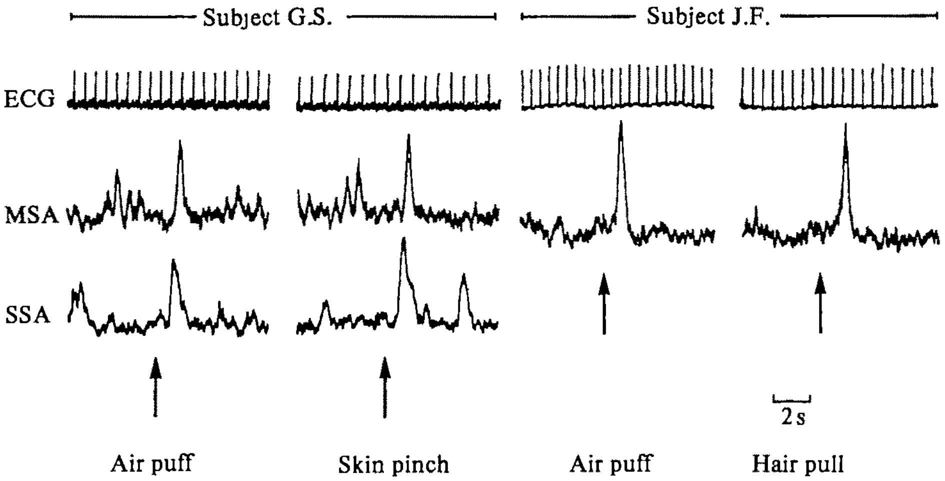


FIG. 3. Examples of arousal stimuli evoking distinct single bursts of MSA (and SSA) following bilateral block of glossopharyngeal and vagus nerves. Arrows indicate stimulus. Same timescale in all panels. Note that SSA response occurs slightly before MSA response.

latencies were the same before and during the local anaesthesia of the vagus and glossopharyngeal nerves.) MSA arousal latency was about 0.15 s shorter than the ordinary inhibitory MSA latency in both subjects. The inhibitory MSA reflex latencies were the same before the nerve blocking procedure and after the return of pulse synchrony.

After bilateral nerve block there was also an increase in the number of neural bursts when the subject talked (fig. 4). The increases were difficult to observe when the activity was maximal but were seen clearly during the recovery period. In subject J.F., the effect was notable for approximately one hour. A Valsalva manoeuvre was tried but could not be performed as long as glottis closure was paralysed. Later in the experiments a Valsalva manoeuvre resulted in an increase of MSA as is seen under normal circumstances (Delius *et al.*, 1972*b*).

TABLE 2 MEAN REFLEX LATENCIES (IN S)

Subject	*MSA latency at rest*	*SSA latency*	*MSA arousal latency during block*	*MSA latency after return of pulse synchrony*
G.S.	1.22	0.72*	1.07	1.24
J.F.	1.34	0.83**	1.20	1.38

* Identical SSA latency before, during and after anaesthetic procedure ** SSA latency determined from separate recording at the same site of the peroneal nerve.

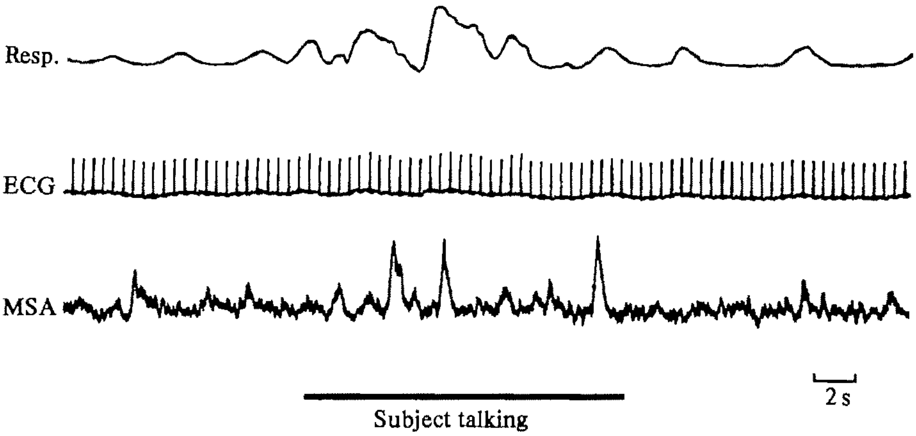


FIG. 4 Increase of MSA, not linked to cardiac rhythm, elicited by talking, in subject J F. 10 min after bilateral block of glossopharyngeal and vagus nerves. Resp. = respiration.

MSA Rhythms during the Peak of Activity

During the first few minutes following bilateral nerve block the pattern of MSA was similar to that of SSA (fig. 1, fifth panel), with bursts of varying duration appearing in a slow irregular rhythm. Activity in skin and muscle fascicles (subject G.S.), however, did not become synchronous. From a manual analysis of the MSA rhythms during this period (measuring distances between successive peaks in the mean voltage neurogram), the dominating frequency was found to be approximately 0.6 Hz in both subjects. Results of power spectral analysis of the mean voltage nerve signal are summarized in fig. 5. Before anaesthesia, MSA showed a frequency peak corresponding to the heart rate, as expected (fig. 5A). The first minute after disappearance of overt pulse synchrony (fig. 5B and B1), no peak related to the cardiac rhythm was seen, the frequency spectra being similar in both subjects with a few major peaks between 0.4 and 0.7 Hz. Fig. 5B2 shows the frequency spectrum of SSA during the same period—there was an apparent similarity to MSA, although with a higher proportion of still slower frequencies in SSA (the power spectrum of SSA was essentially the same throughout the experiment). Later during the bilateral nerve block, major MSA frequency peaks became more evenly distributed between 0 and 1 Hz in both experiments. During the recovering phase the frequency pattern returned successively to the initial appearance, as illustrated by fig. 5C. (Because different amplification was used in different analyses, peak amplitudes are not comparable between all spectra shown. The relatively high amount of low frequencies in A and C (subject J.F.) depends on the low amount of MSA related energy, which makes the low-frequency noise relatively strong, although it is of little significance. The spectra in B1 and B2 (G.S.) and B (J.F.) can be compared more

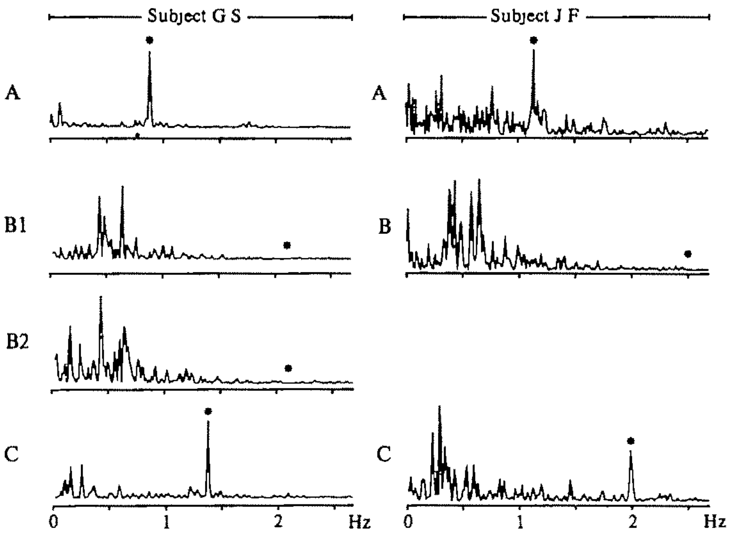


FIG. 5. Frequency spectra of mean voltage neurograms. A: MSA. Control before nerve block. Main peaks, 0.89 Hz and 1.14 Hz (asterisks) respectively, correspond to heart rate (54 and 68 beats/min). B1 and B: MSA; B2. SSA. Second minute following bilateral block of glossopharyngeal and vagus nerves. Main peaks in B1 and B2 0.45 and 0.65 Hz (subject G.S.); main peaks in B 0.48 and 0.65 Hz (subject J.F.). Peak corresponding to heart rate is lacking (130 and 150 beats/min respectively; indicated by asterisks). C: MSA after return of pulse synchrony Main peaks, 1.38 and 2.00 Hz (asterisks) respectively, correspond to heart rate (83 and 120 beats/min) Different amplification in different analyses—peak amplitudes not comparable between spectra

closely, since there was a large amount of burst-related energy and the amplification was similar in these analyses.)

Inspection of MSA and SSA mean voltage neurograms (subject G.S.) following bilateral nerve block showed that many bursts of MSA were preceded by a burst of SSA. Measurement of the delay from the peak of a burst of SSA to the peak of the next burst of MSA (if occurring within 1 s) showed an approximately gaussian

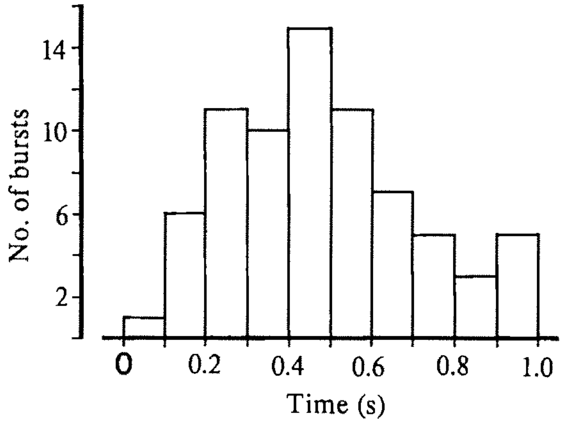


FIG. 6. Subject G.S. Distribution of delay (peak-to-peak) from burst of SSA to subsequent burst of MSA, if occurring within 1 s. Analysis comprises bursts occurring during the first 3.5 min after total loss of cardiac rhythmicity. Mean delay 0.45 s (SD 0.22 s), n = 74. Note that during the same time period 18 bursts of SSA occurred without succeeding burst of MSA; 30 bursts of MSA occurred without a preceding burst of SSA.

distribution (fig. 6) with a delay of 0.45+0.22 s (mean+SD). Note, however, that only about 60 per cent of the bursts showed this kind of coupling. On cross-correlation a low peak arose, corresponding to an average delay of 0.45 s from SSA to MSA.

DISCUSSION

Pathways Affected by the Anaesthesia

Judging from the abolition of somatic nerve functions, the vagus and glossopharyngeal nerves were affected by the anaesthesia. Obviously baroreceptor afferent fibres were blocked. Block of chemoreceptor afferents may have contributed to the effects recorded, although possibly to a minor extent, since stimulation of chemoreceptors in animal experiments causes vasoconstriction, increased blood pressure and decreased heart rate. Thus blocking of afferent chemoreceptor activity would tend to counteract an increase of blood pressure (Folkow and Neil, 1971). Pulmonary afferent pathways are also blocked by the present procedure (Guz *et al.*, 1966). They contain fibres from baroreceptors and stretch receptors; whether the latter contribute to our results is uncertain. Afferent baroreceptor activity from liver and intestine probably does not use the ninth and tenth nerves as main pathways (Andrews *et al.*, 1972; Kostreva *et al.*, 1980). Thus it seems safe to conclude that our results are due mainly to blocking afferent activity from carotid, aortic and cardiopulmonary baroreceptors.

Muscle Sympathetic Activity

The main effects of the nerve blocks in the neck were (1) a strong increase of MSA with loss of cardiac rhythmicity, accompanied by hypertension and tachycardia; (2) similarity but not identity of MSA and SSA patterns; (3) reflex discharges occurring in MSA following arousal stimuli. The increases of heart rate and blood pressure were similar to those reported previously in man after local anaesthesia of the glossopharyngeal and vagus nerves (Mushin, 1945; Lampen *et al.*, 1949; Guz *et al.*, 1966). Both those changes and the increase of MSA were expected in view of the well-known inhibitory reflex effects of arterial and cardiopulmonary pressure receptors. For example, in animals baroreceptor deafferentation leads to increased activity in several different sympathetic nerves (Gernandt *et al.*, 1946; Iggo and Vogt, 1962; Koizumi *et al.*, 1971). In man, baroreceptor unloading, induced by changing posture from lying to upright (Burke *et al.*, 1977) or by applying lower body negative pressure (Sundlöf and Wallin, 1978*b*) regularly increases the level of MSA. In the present experiments cardiac rhythmicity of MSA was lost in both subjects during the anaesthesia and instead, frequent discharges of irregular duration and strength occurred at rates of 0.4 to 0.7 Hz. This activity is probably a human counterpart to the irregular rhythmic sympathetic activity recorded after baroreceptor denervation in animals (Bronk *et al.*, 1936; Alexander, 1945; Weidinger *et al.*, 1961; Downing and Siegel, 1963; Koizumi *et al.*, 1971; Gebber, 1980). The explanation for the preservation of cardiac rhythmicity during the first minute after bilateral anaesthesia in subject G.S. is probably that during this phase the nerve block was only partial, so that inhibition from arterial baroreceptors responding to the systolic blood pressure peaks was still present.

After complete baroreceptor denervation in cats there was an irregular 2 to 6 Hz rhythm (i.e. close to the heart rate) in preganglionic splanchnic and postganglionic renal nerves (Taylor and Gebber, 1975; Barman and Gebber, 1980). The rhythm was abolished in spinal cats (McCall and Gebber, 1975) but persisted after midcollicular decerebration (Barman and Gebber, 1980), indicating that the activity was generated in the brainstem. The 2 to 6 Hz rhythm was observed in a 1 : 1 relationship in different postganglionic sympathetic nerves after baroreceptor denervation (Gebber and Barman, 1980). In our experiments, MSA was not recorded simultaneously in different limb nerves, but the strong 1 : 1 relationship of normal human MSA rhythms in different nerves (Sundlöf and Wallin, 1977) and the above animal findings suggest that the 0.4 to 0.7 Hz MSA may be synchronous in different limb muscle nerve fascicles. After baroreceptor deafferentation in cats, sympathetic discharges could be entrained by electrical stimulation of the carotid sinus nerve in the 2 to 15 Hz frequency range (Bronk *et al.*, 1936). Thus an intrinsic rhythm of 2 to 6 Hz in the cat would readily be entrained in the cardiac rhythm by baroreceptor modulation (Taylor and Gebber, 1975), as would probably the present 0.4 to 0.7 Hz activity in man. We therefore hypothesize that in man there is also an intrinsic MSA rhythm (perhaps generated in the brainstem) which is normally entrained in the cardiac rhythm by recurrent inhibitory impulse volleys from the arterial baroreceptors.

In MSA there is under ordinary conditions little or no activity occurring between the pulse-synchronous bursts; there is thus no appreciable continuous sympathetic activity. In the present experiments the background level of activity in the mean voltage neurogram increased in both subjects in conjunction with the anaesthesia. This is, however, no safe indication of continuous sympathetic activity since during that phase of the experiment the subjects may have developed unnoticed muscle tension, so that the increased level may have been due to increased afferent mechanoreceptive activity or possibly a minute change of recording site. When the number of bursts in the mean voltage neurogram (which would not be affected much by such artefacts) was compared between the two subjects during the first minute after loss of cardiac rhythmicity, there was no appreciable difference (fig. 2). Before the block there was a clear difference in burst incidence; thus interindividual differences in the 'level' of MSA at rest (Sundlöf and Wallin, 1977) are probably due to different degrees of peripheral inhibition (presumably from high and/or low pressure receptors) rather than to differences in central sympathetic drive.

Skin Sympathetic Activity

Subject G.S. had a high outflow of SSA (fig. 1), probably explained by emotional stress caused by the experimental design. On inspection of the mean voltage neurogram from the skin nerve, no cardiac rhythmicity was detected and neither was there a clear peak corresponding to the heart rate in the frequency spectrum of the neurogram. No increase of SSA was seen following the nerve block. This finding agrees with the lack of effect on SSA from carotid sinus nerve stimulation (Wallin *et al.*, 1975) and supports previous reports of an absent or only weak baroreceptor influence on SSA (Hagbarth *et al.*, 1972).

Arousal Responses in MSA

Normally arousal responses occur readily in SSA (Hagbarth *et al.*, 1972) but not in MSA (Delius *et al.*, 1972*b*). During the anaesthesia arousal stimuli gave rise to distinct reflex discharges in MSA which were strikingly similar to the SSA responses (fig. 3). When the anaesthesia wore off such discharges could no longer be evoked. The increase of MSA evoked by talking (fig. 4) may also be an effect of arousal; normally this can occur in SSA but not in MSA. Consequently, after elimination of afferent inflows in the vagus and glossopharyngeal nerves, not only the spontaneous activities but also the evoked responses in SSA and MSA became more similar than before. If the effect can be ascribed to loss of baroreceptor input it would mean that such input, in addition to being responsible for the characteristic discharge pattern in MSA, also serves as a powerful brake on reflex effects evoked from other types of inputs. A possible site of such interaction may be the locus coeruleus, which has been ascribed a role in the regulation of vigilance and arousal reaction (Foote *et al.*, 1983) and which is also influenced by vagal activity from cardiopulmonary baroreceptors (M. Elam, T. Svensson and P. Thoren, personal communication).

The latency to the beginning of the arousal response in SSA was 0.35 s shorter than the corresponding latency in MSA (Table 2). At least in part the difference may be explained by different conduction velocities in postganglionic sympathetic fibres to skin and muscle (Fagius and Wallin, 1980), but whether that is the only reason is unclear. In patients with spinal cord injuries cutaneous stimuli below the lesion evoke spinal reflex discharges which also occur in parallel in skin and muscle nerves but with a latency difference of only 0.05 to 0.15 s (L. Stjernberg and G. Wallin, unpublished). Thus the longer latency difference in the present experiments may be due in part to a longer central (spinal or supraspinal) delay for MSA than for SSA. The difference between latency to bursts of MSA following arousal stimuli and ordinary inhibitory MSA latency (Table 2) may be due to the inclusion of cardiovascular events in the latter (Fagius and Wallin, 1980).

Comparison of Rhythms in MSA and SSA

When cardiac rhythmicity disappeared in MSA the activity consisted of frequent irregular bursts of varying duration, so that the temporal pattern of activity became similar to that in SSA (fig. 1, fifth panel). However, although several bursts occurred approximately in parallel at the two recording sites in subject G.S. and although there were some common peaks in the frequency spectra, the records never became as similar as they normally are in recordings from two muscle nerves (Sundlöf and Wallin, 1977) or from two skin nerves supplying hands or feet (Bini *et al.*, 1980*b*) in unanaesthetized subjects. This may indicate that the central rhythm generators for the two types of activity have some but not all properties in common. Alternatively, there may be a common rhythm generator but the descending outflows may be modulated differently from sources other than those mediated *via* the vagus and glossopharyngeal nerves.

The 0.35 s difference in latency between bursts of SSA and MSA evoked by arousal stimuli may be a clue as to the time lag between related rhythms of MSA and SSA. Other indications support such a temporal relationship: a mean delay of 0.45 s from bursts of SSA to bursts of MSA at manual measurement following bilateral nerve block (fig. 6) and a corresponding peak at 0.45 s in the cross-correlogram. These figures are of the same order, although not identical, which may indicate that the assumed temporal relationship is relatively weak.

Clinical Implications

Interruption of afferent nerve activity, modulating sympathetic outflow, may have consequences of pathophysiological significance. Change of sympathetic discharge patterns following chronic lesions of cat limb nerves was recently reported (Blumberg and Jänig, 1983); after cutting a peripheral nerve, the differences between muscle and skin vasoconstrictor activity were reduced and the patterns became similar in both kinds of nerves. Patients with spinal cord injuries exhibit common properties of MSA and SSA below the level of the lesion (Stjernberg and Wallin, 1983). Such findings and the present results emphasize the possibility of common intrinsic properties of MSA and SSA at different hierarchic levels. The normal differentiation of MSA and SSA may evolve from different afferent influences modulating activity from related central oscillators. Deafferentation at various levels could result in abnormal reflex patterns giving rise to symptoms. Such a hypothesis would be in accordance with other examples of lesions in the nervous system, revealing patterns which normally are concealed by inhibitory regulation, such as the Babinski sign and reflex grasping.

The cardiovascular clinical picture arising from shortlasting baroreceptor deafferentation resembles closely that of tachycardia and hypertension in the Guillain-Barré syndrome (Lichtenfeld, 1971; Goulon *et al.*, 1975). Microneurographic recordings of MSA from such patients have shown a pronounced increase of activity during the illness (Fagius and Wallin, 1983). The activity was synchronous with the pulse and similar to that of subject G.S. during the first minute of bilateral nerve block in the present study, that is, before the block became complete (fig. 1, fourth panel). Thus the assumption of partial baroreceptor deafferentation underlying the transient hypertension and resting tachycardia in the Guillain-Barré syndrome, as discussed in detail by Fagius and Wallin (1983), is supported by the present findings.

ACKNOWLEDGEMENTS

Supported by the Swedish Medical Research Council, grant B83-04X-03546-12B, and the Sätra Brunn Fund for Medical Research.

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(*Received August 7, 1984. Accepted October 23, 1984*)

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POSTTRAUMATIC CERVICAL SYRINGOMYELIA

INCIDENCE, CLINICAL PRESENTATION, ELECTROPHYSIOLOGICAL STUDIES, SYRINX PROTEIN AND RESULTS OF CONSERVATIVE AND OPERATIVE TREATMENT

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SUMMARY

In eleven years, 30 (3.2%) of 951 patients with spinal cord injury developed cervical syringomyelia. This condition was found in 22 (4.5%) of 488 posttraumatic tetraplegic and 8 (1.7%) of 463 posttraumatic paraplegic patients; the incidence was about 8 per cent in patients with complete tetraplegia. This study demonstrated the rarer clinical manifestations of syringomyelia, namely autonomic dysfunction, alterations in the sensory level with postural changes, the early occurrence of tendon areflexia and painless motor deterioration. Prolonged F wave latencies were present in all patients with a demonstrable syrinx and a higher protein content was found in the syrinx than in the cisternal fluid. Some of the symptoms and signs in a proportion of the patients treated conservatively remained stable without operative treatment over a number of years. Most of the patients in whom operation was performed for progressive motor weakness or severe pain had good postoperative results although a few developed late sensory or motor changes. There was no benefit in operating on a patient with a small syrinx.

INTRODUCTION

Posttraumatic syringomyelia can occur under the following circumstances (Barnett, 1973; Barnett and Jousse, 1976): (1) as a late sequel to traumatic tetraplegia and paraplegia; (2) as a late sequel to minor or moderate spinal cord injury; (3) where the trauma appears to precipitate symptoms, or to aggravate a preexisting but unrecognized syringomyelia; or (4) as a late sequel to spinal trauma producing adhesive arachnoiditis. We here report 30 patients who belong to the first group. The purpose of this paper is to show that the incidence of posttraumatic syringomyelia is higher than is generally acknowledged and that the fluid from the cavity differs from cerebrospinal fluid (CSF), to demonstrate the rarer clinical

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presentations and the value of electrodiagnostic investigations, and to assess the results of conservative and operative treatment.

MATERIALS AND METHODS

Patient Population

From May 1, 1973 to March 31, 1984, 488 posttraumatic tetraplegic and 463 posttraumatic paraplegic patients were admitted to the Spinal Cord Injury Center, with the exclusion of those who had nontraumatic myelopathy, spinal fracture without myelopathy, minor cervical trauma, or less than three months follow-up after injury. Most of these patients had been seen by us at least once a year. Of these 951 patients, 937 males and 14 females, the spinal cord injury was complete in 459 and partial in 492. A total of 30 male patients were found to have posttraumatic cervical syringomyelia which was confirmed by metrizamide spinal computerized tomography (CT) and/or gas myelography in 25 patients. The respective incidence of this condition in complete and incomplete paraplegic and tetraplegic patients is shown in Table 1.

TABLE 1 INCIDENCE OF POSTTRAUMATIC SYRINGOMYELIA IN 951 PATIENTS WITH SPINAL CORD INJURY FROM MAY 1, 1973 TO MARCH 31, 1984

No. of cases of syringomyelia	*Spinal cord injury*	*Incidence (%)*
30	All patients (n = 951)	3.2
22	Tetraplegia (n = 488)	4.5
8	Paraplegia (n = 463)	1.7
18	Complete (n = 459)	3.9
12	Partial (n = 492)	2.4
14	Complete tetraplegia (n = 177)	7.9
8	Incomplete tetraplegia (n = 311)	2.6
4	Incomplete paraplegia (n = 181)	2.2
4	Complete paraplegia (n = 282)	1.4

The ages of these 30 patients ranged from 20 to 63 years (mean 43) when the diagnosis of syringomyelia was made. The aetiology of myelopathy was as follows: motor vehicle accidents (18), diving injuries (7), falls (3), military injury (1) and plane crash (1). The spinal fracture was located in the cervical region in 19 patients, cervicothoracic in 3, thoracic in 3, and thoracolumbar in 4; another patient had an injury restricted to the cervical anterior longitudinal ligament without vertebral fracture dislocation. The posttraumatic myelopathy was sensorimotor and complete in 18 patients, sensory incomplete but motor complete in 5 (including 2 with sacral sparing only), and sensorimotor incomplete in 7.

The interval from the spinal injury to the appearance of the first symptoms of syringomyelia ranged from 3 months to 34 years (mean 9 years); the diagnosis was delayed for up to 12 years (mean 2.8 years) after the onset of new symptoms. Including 2 patients who were asymptomatic, the lapse of time from the injury to the diagnosis of this condition ranged from 6 months to 36 years (mean 13.2 years). The average lapse from the injury to the new symptoms was 7.5 years (range 3 months to 23 years) in 16 patients with complete cord lesions and 9.9 years (range 3 months to 34 years) in 12 subjects with partial lesions; it was 8.6 years (range 3 months to 34 years) in 19 patients with cervical fractures and 13.5 years (range 4 to 22 years) in 4 patients with thoracolumbar injury.

Symptoms and Signs

The first complaints, single or combined, and the symptoms at the time the diagnosis of syringomyelia was made, are presented in Tables 2 and 3. Two patients had no symptoms, 7 had a single symptom, 15 had two symptoms, 4 had three symptoms and 2 had four symptoms when the syringomyelia was discovered.

TABLE 2. INITIAL SYMPTOMS OF POSTTRAUMATIC SYRINGOMYELIA IN 30 PATIENTS

Initial symptom	*No. of patients*
Pain	17
Numbness	8
Increased muscle weakness	7
Increased spasticity	3
None	2
Increased sweating	1
Autonomic dysreflexia	1

TABLE 3. SYMPTOMS IN 30 PATIENTS WHEN THE DIAGNOSIS OF POST-TRAUMATIC SYRINGOMYELIA WAS MADE

Symptom	*No. of patients*
Pain	21
Numbness	12
Increased motor deficits	12
Increased spasticity	7
Increased sweating	4
None	2
Autonomic dysfunction	1

The symptom of pain, usually dull aching or burning in character, was mild or severe in intensity. Intermittent or constant, it was located at or above the site of the original spinal injury in 13 patients, above and below the spinal injury in 4, and below the spinal injury in 4. In the 8 patients who had pain below their spinal injury, the posttraumatic myelopathy was complete in 5 and partial in 3. The pain was usually aggravated by coughing, sneezing, or straining, and in 3 patients it was much worse in the sitting than in the lying position. It was consistently more severe after meals in one patient, and in another it became more intense when he was driving on a bumpy road. The symptom of numbness was accompanied by pain in 3 patients, whereas 3 patients had upper limb numbness without pain.

TABLE 4 CLINICAL MANIFESTATIONS IN 30 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

Clinical manifestations	*No. of patients*
Ascending sensory level	28
Depressed tendon reflexes	23
Increased motor deficits	12

Table 4 shows the clinical picture in 30 patients at the time syringomyelia was discovered. The ascending sensory level involved both sides of the body in 22 patients and was limited to one side only in 6. Dissociated sensory loss between pain and proprioception in the ascending segments was seen in all 28 patients, but dissociation between pain and touch was observed in only 21 patients. An alteration in the ascending sensory level was observed with and without postural changes in each of the 3 patients. In 6 patients there was a suspended intact zone between the ascending sensory level and the level of the original spinal cord injury. In 13 patients the first symptom occurred before an ascending sensory level was noticed, while this had been unnoticed in another 13; in 2 patients the ascending sensory level was not associated with any symptoms. In 5 of 12 patients whose posttraumatic myelopathy was incomplete, there was sensory deterioration below the site of their spinal injury. Tendon reflex depression in the upper limbs was bilateral in 8 patients and unilateral in 15. It was observed in the presence of an ascending sensory level in 19 patients, whereas areflexia preceded sensory changes in 4.

Twelve patients noticed progressive weakness of their upper limbs (above the level of their spinal injury), which was bilateral in 7 and unilateral in 5; in 1 of the 7 patients whose posttraumatic myelopathy was sensorimotor and incomplete, there was motor deterioration below the level of the spinal cord injury. Increased motor weakness was the only symptom in 1 patient. It was associated with increased sweating in 3, numbness in 4, pain in 8, an ascending sensory level in 11 and depressed tendon reflexes in 11.

None of our patients had a Horner's syndrome (Shannon *et al.*, 1981), sensory involvement of the face *via* trigeminal nerve innervation (Barnett and Jousse, 1973*a*), decreased respiration upon sitting (Quencer *et al.*, 1983) or other brainstem findings (Vernon *et al.*, 1982), but 2 had neuropathic changes of the shoulder joint.

Electrodiagnostic Evaluation

Electrodiagnostic studies were undertaken on 24 of 30 patients with a clinical diagnosis of posttraumatic syringomyelia, using a TECA TE 4 electromyograph (TECA Corp., Pleasantville, New York). Postoperative studies were performed serially in patients undergoing drainage of the syrinx. Patients treated nonsurgically were evaluated if the clinical picture changed.

Electromyography was performed using monopolar needle electrodes. Motor unit numbers, amplitude and waveform were assessed. F wave latencies were measured using the techniques of Magladery and McDougal (1950). Ten consecutive F waves were measured and the shortest latency recorded. When atrophy of the intrinsic hand muscles made recording from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) impossible, recordings were made from the wrist flexors and extensors while stimulating at the antecubital fossa.

Radiological Studies

Before the introduction of spinal CT, patients with clinically suspected syringomyelia were examined by gas myelography (Rossier *et al.*, 1983). Spinal CT has now supplanted gas myelography in the initial investigation of these patients (Resjö *et al.*, 1979; Rossier *et al.*, 1983). A total of 25 patients were studied by spinal CT and/or gas myelography; 18 underwent spinal CT and 17 gas myelography; 13 had either spinal CT or gas myelography and 10 had both studies.

The techniques for spinal CT and gas myelography have been described previously (Rossier *et al.*, 1983). CT of the cervical and upper thoracic spine, and the lower thoracic spine when indicated, was carried out with a Siemens Somatom II high-resolution scanner or a fourth-generation Delta 2010 scanner. Plain spinal CT without intraspinal metrizamide was performed in 4 patients only. All 18 patients were examined immediately or within 24 h (usually within 8 h) after a C1-2 injection of 4 to 8 ml of metrizamide (160–200 mg/dl), with the exception of 2 patients who had a lumbar puncture; 15 patients were scanned twice and 3 were scanned three times. The slice thickness was 2 to 4 mm. Scanning was performed in all 18 patients in the supine position and in 1 patient also in the left lateral position; 2 patients were restudied after the syrinx was shunted to the subarachnoid space. The presence of a low-attenuation area within the cord in plain CT views, or a high-density zone with intrathecal metrizamide in two or more consecutive scan slices in the absence of surrounding artefacts, was considered as evidence of cystic formation within the spinal cord. A cursor was used in 4 patients to measure and compare the densities (in Hounsfield units) in the subarachnoid space, the spinal cord, and the intramedullary cavity before and/or after injection of the contrast material. CT did not reveal extension of the cyst into the posterior cranial fossa.

Gas myelography was performed under general anaesthesia. The patient was placed in the right lateral position on the polytome table, tilted head down 10 to 15 deg. After removal of 80 to 100 ml of CSF, 60 to 100 ml of oxygen was introduced into the spinal canal *via* a C1-2 puncture to fill the entire subarachnoid space. In 1 patient, 200 ml of oxygen was introduced and in another, the gas was introduced into the subarachnoid space *via* lumbar puncture. Lateral tomograms of the cervical, thoracic and lumbar regions of the spine were made; cuts were obtained at 2 mm intervals. Filming was repeated in the head-flat position in 16 patients and in the 5 to 15 deg head-up position in 3. At the end of the procedure, the patient was rolled into the horizontal supine position and remained in bed in a slightly head-down position for at least 24 h. Gas myelography was repeated in 3 patients after shunting of the syrinx.

Overall Management

Nineteen patients were treated conservatively and 11 surgically. Of the patients who were not operated upon, 1 had episodes of autonomic dysfunction only without sensory or motor deficits, 2 had no symptoms, 2 had a very incomplete posttraumatic myelopathy, 3 refused radiological procedures, 3 had no pain, and 8 had pain but without motor weakness. The length of follow-up ranged from 9 months to 12 years (mean 4.1 years) after the onset of new symptoms in 15 patients; 2 patients who had no symptoms and 2 patients who developed symptoms before they were seen by us had a follow-up that ranged from 1 to 4 years (mean 1.8) after the diagnosis of syringomyelia. Of these 19 patients, 10 had pain, 18 had an ascending sensory level, 13 had depression of tendon reflexes and 4 had increased motor weakness.

Operative drainage of the cavity was performed in 11 patients. The postoperative follow-up ranged from 1.5 to 8 years (mean 4.9) in 9 patients. Another 2 patients had been followed for less than 6 months after their operation. Of these 11 patients, 9 had pain, 10 had an ascending sensory level, 10 had depression of tendon reflexes and 8 had increased muscle weakness. The indications for surgical intervention were loss of motor function and severe pain. Eight patients were operated upon once and 3 twice because of early or late neurological deterioration. Excluding 1 patient whose complete operation report was not available, the syrinx was shunted to the subarachnoid space with a silastic T (fig. 1) or K tube (fig. 2) in 10 patients. A total of four T and seven K tubes were used. Each shunt measured 1.3 mm external diameter and 0.8 mm internal diameter except for one T tube which measured 2.31 mm external diameter and 1.6 mm internal diameter. A silastic sponge-like post was used in 1 patient because the intended shunt was found to be too large for the syrinx at the operation.

Operative Procedure

The complete operation note was available in 10 patients. A single or double-level laminectomy, with the patient prone and the neck flexed, provided sufficient exposure for insertion of the shunt in all 10 patients, except for 1 who was operated upon in the sitting position because he was obese and could not be positioned satisfactorily prone on the operating table. The laminectomy was carried out between C5 and C7 where the spinal cord appeared the widest in the gas myelogram in 3 patients whose original spinal injury was located in the thoracic or thoracolumbar region. In 7 patients who had a spinal fracture in the cervical or cervicothoracic region, the laminectomy was performed above and well away from the site of the spinal injury. The dura was opened without disturbing the arachnoid and its margin was sewed to the neck muscles. On opening the arachnoid, the syringomyelia appeared large in 8 patients and small in 2. The dorsal part of the cord appeared stretched or even grey due to the underlying cyst in 5 patients, and normal in 5. A 25 gauge needle was passed into the cavity and a few millilitres of fluid were withdrawn for analysis, except for 1 patient who had a very small cyst. A 3 to 6 mm incision was made in the midline in 9 patients and on the left side in 1 who had a small syrinx. The intramedullary arm of the shunt was trimmed to the size of the cavity so that after insertion, it could be moved up and down slightly within the cyst without difficulty, indicating that it was not kinked or jammed against the ends of the syrinx. The cord expanded after fluid was instilled into the cyst through the shunt and some of the fluid came out of the cord around the shunt. The spinal cord also collapsed after the fluid was aspirated *via* the shunt, indicating that the intramedullary arm of the T or K tube was in a good position. The extramedullary arm of the shunt was trimmed to between 1.8 and 5 cm in length and inserted cranially into the subarachnoid space beyond the site of the dural incision and away from the spinal injury in 10 patients. The arachnoid was left open but the dura was

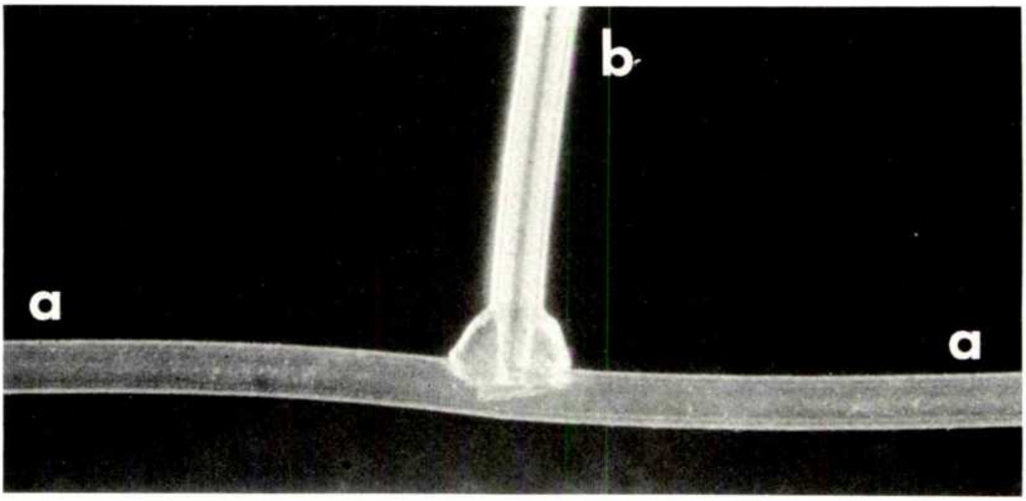


FIG. 1. Silastic T tube with an intramedullary arm (a) which is placed inside the syrinx and an extramedullary arm (b) which is inserted into the subarachnoid space. It measures 1.3 mm external diameter and 0.8 mm internal diameter.

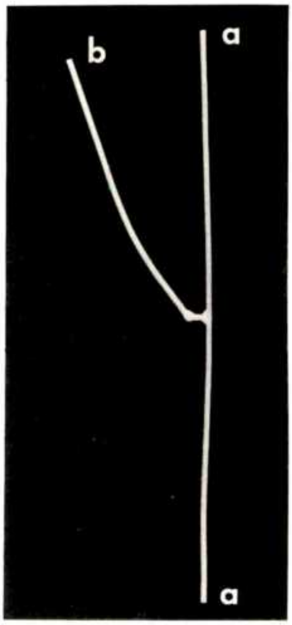


FIG. 2. Silastic K tube (Holter-Hauser International, Bridgeport, Philadelphia) with an intramedullary arm (a) which is placed inside the syrinx and an extramedullary arm (b) which is inserted into the subarachnoid space. It measures 1.3 mm external diameter and 0.8 mm internal diameter.

tightly closed. An operating microscope was not used during the procedure; magnifying lenses of 3.5 power were found to be quite adequate.

RESULTS

Electrodiagnostic Findings

Preoperative electrodiagnostic abnormalities included changes characteristic of a diagnosis of syringomyelia, coincidental static root lesions and neuropathies, as well as the presence of peripheral nerve entrapments and F wave abnormalities.

Electrodiagnostic changes supporting a diagnosis of syringomyelia were the loss of motor unit numbers in at least two root distributions and an increase in motor unit amplitude and duration consistent with reinnervation. Fibrillation potentials and positive sharp waves were infrequently seen suggesting a very slow progression of the process.

Forty per cent of the patients studied had concomitant evidence of entrapment. At least one peripheral nerve was involved and in some cases multiple nerves in the upper limbs were implicated. Six median nerves showed evidence of entrapment at the flexor retinaculum on the basis of prolonged sensory and motor latencies. One median nerve showed only a prolonged sensory latency. Ulnar involvement was seen at the level of the cubital tunnel in 4 patients (on the side of the syrinx). Slowing only in the elbow to wrist segment was present in 2 other patients. These abnormalities did not improve in patients who underwent drainage of the syrinx. Two patients had prolonged latencies to the deltoid muscle on axillary nerve stimulation. Both patients improved after drainage of the cyst.

TABLE 5. F WAVE LATENCIES (SHORTEST LATENCY RESPONSE OF 10 RESPONSES MEASURED)

	Median	*Ulnar*
Normal controls (n = 9)	27.1 ± 1.4 ms	27.9 ± 1.2 ms
Spinal cord injured patients without suspected syringomyelia (n = 9)	27 ± 2.5 ms	27.5 ± 2 ms
Patients with documented syrinx and in whom F wave responses could be recorded (n = 9)	31.1 ± 2.9 ms	30.1 ± 1.6 ms

TABLE 6. F WAVE LATENCIES (IN MS) IN PATIENTS TREATED SURGICALLY

Preop 8.10.79	31.3 (L ulnar)
Postop 9.13.82	28
Preop 1.16.81	34.3 to FCR
Postop 11.18.82	22.4 to FCR (now able to record F wave at 35 ms from APB)
Preop 10.14.81	17.1 to FCR (no response from APB)
Postop 1.31.83	29.6 to APB
Preop 6.17.81	29.2
Postop 10.14.81	27
Preop 3.26.82	31.7 (L median) 32.6 (L ulnar)
Postop. 8.31.82	34.0 (L median). No response (L ulnar)

FCR = flexor carpi radialis. APB = abductor pollicis brevis.

F wave latencies were prolonged in all patients with a documented syrinx. Table 5 shows F wave latencies in median and ulnar nerves in asymptomatic able-bodied age-matched controls, in patients with spinal cord injuries but no symptoms suggestive of a syrinx and in patients with syringomyelia in whom F wave measurements could be made from the intrinsic hand muscles. There were 4 patients who were not included because of severe atrophy of abductor pollicis brevis and abductor digiti minimi. This makes the F waves in patients with syrinx appear faster than they actually were in our population. Five patients had serial F wave measurements made after drainage of the syrinx. All but one had some improvement in F wave latency (Table 6). It can be seen that recovery of the F wave response is consistent and corresponds to an increased motor unit count postoperatively. In patients who did not undergo surgical drainage there was either no improvement or deterioration of the F wave response (blocking or loss of the response) during the period of follow-up.

Radiological Findings

The results of spinal CT and gas myelography in our first 15 patients were reported elsewhere (Rossier *et al.*, 1983).

Table 7 shows the results of spinal CT in 18 patients. Enhancement of the cyst up to 8 h postmetrizamide was seen in 16 patients but this was absent in 2. The syrinx appeared as a large single collection of dye in 13 patients (Rossier *et al.*, 1983) and in the form of small multiple collections of dye in 3 patients (fig. 3). Of the 5 patients who had an enlarged cord by CT, only 1 showed no evidence of dye collection in the cord. Four patients who were scanned 24 h postmetrizamide did not present any sign of dye uptake in the cord substance. Postoperative metrizamide spinal CT in 2 patients revealed stasis of the dye within the cyst; in 1 patient it also showed a decrease in the size of the cyst. One patient experienced less pain and leg spasms after spinal CT, which was, however, transient.

TABLE 7. SPINAL CT FINDINGS IN 18 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

	Cases	
Spinal CT findings	*No.*	*Percent*
Plain spinal CT	4	100
Intramedullary translucent areas	3	75
Spinal CT with metrizamide	18	100
Size of spinal cord:		
Widened	5	27.8
Normal	2	11.1
Atrophic	11	61.1
Enhancement of cyst	16	88.9

TABLE 8. GAS MYELOGRAPHIC FINDINGS IN 17 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

	Cases	
Gas myelographic findings	*No.*	*Percent*
Generalized cord enlargement	12	70.6
Localized cord enlargement	5	29.4
Collapsing cord sign	7	41.2

Gas myelography (Table 8) showed generalized enlargement of the cervical cord in 12 patients (Rossier *et al.*, 1983) with extension into the thoracic region in 2 and a localized cord enlargement in 5 patients. The localized swelling was noted at the site of the original spinal injury in 2 patients and above it in 3. Of these 5 patients with focal cord enlargement, the rest of the cervical cord appeared normal in 1 and atrophic in 4. Collapsing cord sign was seen in 7 patients. The spinal cord enlargement was greater in the head-flat than in the head-down position in 5 patients; the cord swelling disappeared and the gas myelogram disclosed an atrophic cord in the head-down position in 1 patient and this occurred in the head-up position in another. In the other 10 patients, modification of the position did not result in a change of the cord swelling. Postoperative gas myelography in 2 patients showed a collapse of the cystic cord, which then appeared atrophic. One patient experienced persistent left leg pain and another 2 had transient relief of leg spasms after gas myelography.

Ten patients underwent both spinal CT and gas myelography. Metrizamide spinal CT revealed enhancement of the cyst in 9 patients and it demonstrated an enlarged cord in 4 and a small cord in 6, whereas gas myelography revealed an

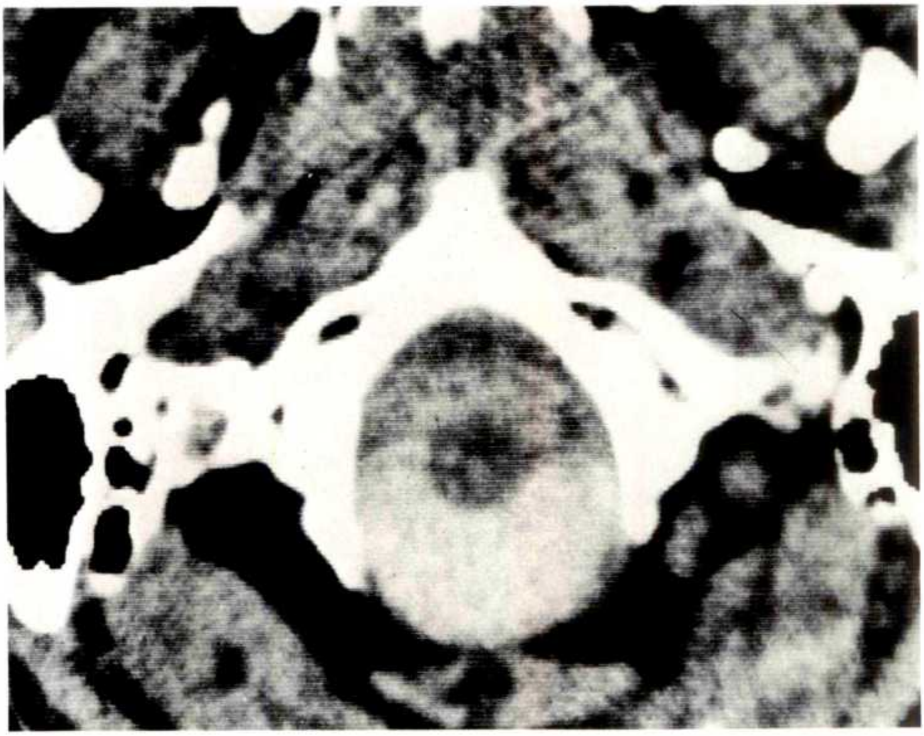


FIG. 3. Spinal CT scan showing small collections of dye within the spinal cord at the upper part of C1 3 h after intraspinal injection of metrizamide.

enlargement of the cord in all 10 patients. The upper level of the cystic lesion shown by the CT scan corresponded with that shown by gas myelography in 4 patients; this correlation was not observed in the other 5 patients.

Protein Content in the Syrinx and Subarachnoid Space and Review of the Literature

Fluid from the syrinx was available for analysis in 9 of the 11 patients who had the shunting operation. As 3 patients were operated upon twice, a total of 10 samples of syrinx fluid was examined. CSF from C1-2 subarachnoid space was obtained in 7 patients who had gas myelography or spinal CT prior to the shunting procedure. One patient had a lumbar puncture and in another, the CSF was not obtained for analysis. The syrinx fluid appeared clear in 5 instances, slightly yellow in 3 and slightly pinkish in 2. The protein level in the syrinx was higher than that in the C1-2 subarachnoid space in all the patients (Table 9), including a patient (Case 8) who had gas myelographic evidence of communication with the fourth ventricle (Rossier *et al.*, 1983). The former ranged from 0.35 to 3.9 g/l (mean 1.15) whereas the latter ranged from 0.1 to 0.44 g/l (mean 0.24).

Table 10 shows the results of the analysis of the protein content in the syrinx and

TABLE 9. PROTEIN CONTENT IN THE SYRINX AND CEREBROSPINAL FLUID IN 9 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

Patient	*Syrinx protein (g/l)*	*CSF protein (g/l)*
1	0.35	0.17 (C)
2	0.53	0.10 (C)
3	0.61	0.19 (C)
4	0.66	0.46 (L)
5	0.73	0.44 (C)
6	Second operation: 0.80	0.21 (C)
	First operation: 0.97	0.27 (C)
7	1.26	0.37 (C)
8	1.67	NA
9	3.90	0.20 (C)
Mean	1.15	0.24 (C)

C = cisternal; L = lumbar; NA = not available.

TABLE 10. PROTEIN CONTENT IN THE SYRINX AND CSF AS REPORTED IN THE LITERATURE

Authors	*Syrinx protein (g/l)*	*CSF protein (g/l)*
Barnett and Jousse (1973*a*)	2.24 (faint yellow)	0.24 (C)
	2.00 (faint yellow)	1.35 (C) postmyelogram
	0.38	15.00 (L)
	0.32	0.22 (C)
Foster (quoted by Barnett and Jousse, 1973*a*)	0.71	0.14 (C)
Freeman (1959)	1.30 ('cloudy white fluid')	
Laha *et al.* (1975)	1.00	
	0.90	
	0.65	
Nurick *et al.* (1970)	0.55	0.20 (C)
Werner *et al.* (1969)	0.77	0.28 (C)
	0.37	0.29 (L)
	0.28	0.28 (C)
Mean	0.88	0.18 (C)*

*Excluding the second case of Barnett and Jousse (1973*a*) as the CSF was obtained after myelography. C = cisternal. L = lumbar.

the corresponding CSF given by the other authors in the literature. The syrinx protein ranged from 0.28 to 2.24 g/l (mean 0.88), while the cisternal CSF protein ranged from 0.14 to 0.28 g/l (mean 0.8).

Conservative Treatment

Nineteen patients were treated conservatively. In 6 who had been followed for 3 years or less since the onset of symptoms or the diagnosis of syringomyelia, there was no observable neurological change. The other 13 patients showed either new symptoms or progression of their deficit over the years (Table 11). In 1 patient who first presented with increased motor weakness, motor function became stable for 10 years before further deterioration and in another, motor power became stable after an initial period of progression over 5 years. The follow-up period in these 13 patients who developed new symptoms or progression of the old symptoms was more than 3 years after the onset of symptoms of syringomyelia or its diagnosis, with the exception of 1 patient. None of the 19 patients progressed to the state of 'quadriplegic helplessness' as described by Barnett and Jousse (1973*a*) or severe disability.

TABLE 11. RESULTS OF CONSERVATIVE TREATMENT OF 19 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

	Patients showing deterioration	
Symptom or sign	*No.*	*Percent*
Pain (n = 10)	4	40
Ascending sensory level (n = 18)	8	44.4
Tendon reflex depression (n = 13)	5	38.5
Increased motor weakness (n = 4)	3	75
New symptoms (n = 19)	6	31.5

Operative Results

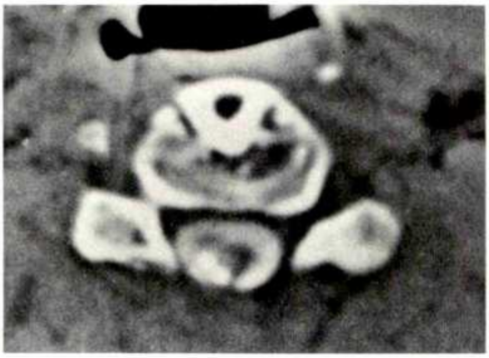
Early postoperative recovery was seen in 9 patients (Table 12). Complete or almost complete pain relief was observed in 8 of 9 patients; another patient had slight pain improvement only. Complete or almost complete motor recovery was noted in 5 of 8 patients; another patient had marked improvement of the wrist extensors but only slight motor return of the triceps which was affected several years before the wrist extensors were found to be weak. The preoperative duration of pain ranged from 4 months to 6 years (mean 2 years) and the preoperative duration of motor deficits was less than 1 year, with the exception of 2 patients who had motor deficits for 4 and 6 years before the operation, respectively. Only 3 of 10 patients showed an improvement of the sensory level by about 3 segments and 1 of 10 patients had an improvement of the tendon reflexes in the upper limbs.

TABLE 12. RESULTS OF SURGICAL TREATMENT OF 11 PATIENTS WITH POSTTRAUMATIC SYRINGOMYELIA

	Patients showing improvement	
Symptom or sign	*No.*	*Percent*
Pain (n = 9)	8	88.9
Ascending sensory level (n = 10)	3	30
Tendon reflex depression (n = 10)	1	10
Increased motor weakness (n = 8)	5	62.5

Transient postoperative bilateral neck, shoulder, and arm pain was seen in 3 patients. Early postoperative neurological deterioration was noted in 2 patients. In the first patient, who was operated upon earlier in this series by another neurosurgeon before the T or K tube was introduced by one of us (J.S.), the syrinx was shunted to the subarachnoid space with a silastic T tube, measuring 2.31 mm external diameter and 1.6 mm internal diameter. The spinal cord lesion of the patient, which was grossly incomplete preoperatively, became complete after the operation. Reexploration of the spinal cord several days later revealed no compression of the cord by the shunt and no evidence of intraspinal bleeding. The extramedullary arm of the shunt was shortened. Postoperatively, there was no recovery but the condition of the patient became stable. Another patient was operated upon in the sitting position as he was obese and could not be positioned prone on the operating table. The syrinx which was shown to be small by gas myelography was collapsed in the upright position and there was some difficulty in finding the cavity. Although only a tiny K tube was inserted, this patient was found to have sensory, reflex and motor deterioration after the operation. He subsequently regained some motor functions but there was no sensory or motor return.

Late neurological deterioration was noted in 3 patients. In the first patient, a silastic sponge-like post (6 mm high, 3 mm long and 2 mm wide) was placed in the cavity and was covered with a layer of arachnoid membrane. This patient had remarkable postoperative improvement of his left postauricular pain and left hand motor function. However, 15 months later, there was recurrence of left ear pain and left hand muscle weakness. Gas myelography revealed enlargement of the cord below the laminectomy site (C5-6) of the previous operation. Another operation was performed and a small T tube (fig. 1) was inserted into the syrinx at C7. Postoperatively, the patient had complete pain relief but no motor return. Two years later, he was found to have a higher sensory level. The second patient did very well after his first shunting operation in 1981 with complete pain relief and complete motor recovery. In March and May, 1983, he underwent a posterior and anterior fusion of the cervical spine for instability. In the early part of 1984, the patient noticed recurrence of left ear pain and right wrist weakness. Spinal CT 45 min after intraspinal injection of metrizamide revealed enhancement of a small cyst at C5 (fig. 4) but a larger cavity just below it at C5-6 (fig. 5), suggesting inadequate drainage of the lower part of the cyst. Gas myelography was not satisfactory at this level where the anterior and posterior subarachnoid space could not be clearly visualized. A further exploration of the spinal cord was performed at C4 and C5, the site of the previous shunting operation. The extramedullary arm of the shunt, including the opening at its end, was covered with a fine layer of scar tissue but the intramedullary arm was patent and a persistent syrinx cavity was found. The original K tube was removed and a new one was inserted into the cavity, passing the long extramedullary arm of the shunt cranially into the subarachnoid space well away from the site of the first shunting operation. The patient had some pain relief but no motor return after this operation. In the third patient, the T tube was suspended from the dura and occluded, functioning as a seton to keep the myelotomy open and to allow the cyst fluid to drain into the subarachnoid space.



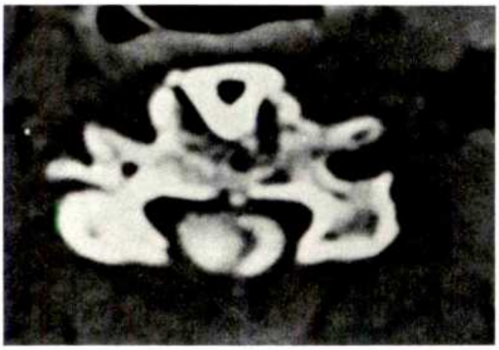


FIG. 4 (*left*). Spinal CT scan 45 min after intraspinal injection of metrizamide showing both limbs of K tube visible with some dye in the cyst at C5. The subarachnoid space is seen all around the cord. FIG. 5 (*right*). Same patient as in fig. 4. Spinal CT 45 min after intraspinal injection of metrizamide showing a large cavity containing the K tube at C5-C6 on the right side of the cord with the subarachnoid space being visible only on the left side. A thin slice of cord tissue is seen on the left between the cavity and the subarachnoid space suggesting that the cyst is not well drained.

Postoperatively, his left arm pain and left shoulder weakness disappeared. However, 7 years later, his sensory level was found to have ascended but without the development of other symptoms.

DISCUSSION

Incidence

The incidence of posttraumatic syringomyelia, 3.2 per cent, in our series is higher than that mentioned in a previous publication (Rossier *et al.*, 1981) or the 1 to 1.2 per cent reported in the literature (Barnett and Jousse, 1973*a*; Watson, 1981). Barnett and Jousse (1973*a*) noted an incidence of 1.8 per cent in the posttraumatic paraplegic and 0.2 per cent in the tetraplegic patients. Of the patients described by Shannon *et al.* (1981) and Vernon *et al.* (1982), syringomyelia was much more often seen in patients with thoracic spinal injury than in those with cervical fractures. All 15 patients reported by Watson (1981) had thoracic or thoracolumbar spinal cord injury. On the other hand, of the 16 patients described by Quencer *et al.* (1983), 12 had cervical and 4 had thoracic cord injury; however, the authors did not determine their incidence of syringomyelia. In our series, the incidence (Table 1) was higher ($P < 0.01$) in the patients with posttraumatic tetraplegia (4.5%) than in those with paraplegia (1.7%). The incidence was much higher in the patients with complete tetraplegia (7.9%) than in those with incomplete tetraplegia (2.6%), incomplete paraplegia (2.2%), or complete paraplegia (1.4%). The incidence was higher in the patients who had a complete spinal cord injury (3.9%) than in those with partial lesions (2.4%) but the difference is statistically insignificant ($P = 0.19$); Griffiths and McCormick (1981) and Quencer *et al.* (1983) did not detect any relationship between the incidence of syringomyelia and the presence of complete or incomplete spinal cord injury.

Onset of Symptoms

Similar to the observations of Werner *et al.* (1969), Barnett and Jousse (1973*a*), Shannon *et al.* (1981) and Vernon *et al.* (1982), the symptoms of syringomyelia could occur as early as 3 months after the trauma or as late as 32 years postinjury. Two patients of ours who had no symptoms were found to have this condition 30 and 36 years postinjury. Barnett and Jousse (1973*a*) noted that the patients with complete cord lesions had an earlier onset of symptoms than those with partial lesions but Shannon *et al.* (1981), Vernon *et al.* (1982) and Quencer *et al.* (1983) did not notice any significant difference in the lapse of time from the injury to the new symptoms in these patients with complete and incomplete lesions. Our findings suggest that, on the average, the patients with complete cord injury had an earlier onset of symptoms than those with partial lesions (7.5 years *vs* 9.9 years) but the difference is not statistically significant ($P = 0.42$). Barnett and Jousse (1973*a*), Williams *et al.* (1981) and Quencer *et al.* (1983) noted no correlation between this latent period and the site of the original spinal injury. Our observations suggest that the average lapse from the injury to the symptoms of syringomyelia was longer in the patients with thoracolumbar injury than in those with cervical fracture (13.5 years *vs* 8.6 years). However, the difference is not statistically significant ($P = 0.39$) as there were only 4 patients with thoracolumbar injuries but 19 patients with cervical fractures.

Clinical Presentation

The common complaints, in descending orders of frequency, were pain, numbness, increased muscle weakness and increased spasticity (Table 2). While the symptom of pain was usually increased with straining, coughing or sneezing, in 3 patients it was worse in the sitting than in the lying position. Quencer *et al.* (1983) suggested that this could be caused by gravitational forces on the lower part of the cyst, resulting in focal stretching of the spinal cord. The pain could be dull aching and constant in the neck or behind the ear and at the same time burning and intermittent in the upper limbs. It was generally located at or above the site of the original spinal injury but occasionally was referred to the abdomen or leg which was below the spinal injury. In 3 patients, the first and chief complaint was the recent onset of severe pain in the abdomen (below the level of their complete spinal cord injury). Subsequently they were found to have an ascending sensory level and impaired tendon reflexes in the upper limbs and the diagnosis of syringomyelia was confirmed by spinal CT. Numbness, as a symptom, was associated with pain most of the time and increased spasticity was rarely the first complaint.

An ascending sensory level was present in almost all patients with syringomyelia, but in 2 patients there was no change in their posttraumatic sensory level when this condition was discovered. Dissociated sensory loss between pain and proprioception within the ascending sensory segments was noted in 28 patients, whereas dissociation between pain and touch was seen in 19 only because of the involvement of the dorsal root entry zone and also because touch sensation, unlike proprioception, is mediated by fibres in the anterior, lateral and dorsal columns. An ascending sensory level was frequently associated with depressed upper limb reflexes but areflexia occasionally preceded sensory changes.

Increased motor weakness was not a constant finding in our patients. It was almost invariably accompanied by an ascending sensory level and loss of tendon reflexes whereas painless progression of motor deficits was uncommon. Barnett and Jousse (1973*a*) and Vernon *et al.* (1982) observed that the vast majority of their patients had unilateral sensory, motor or reflex deficits, whereas most of our patients had bilateral sensory or motor involvement when their syringomyelia was discovered.

Barnett and Jousse (1973*a*), Shannon *et al.* (1981) and Vernon *et al.* (1982) noted that syringomyelia seldom presented as sensory or motor deterioration below the level of the original spinal injury. Five of our 12 patients whose posttraumatic sensory deficits were incomplete had further loss of sensation below the spinal injury and 1 of our 7 patients whose posttraumatic motor deficits were incomplete had motor deterioration below the spinal injury. However, none of our patients had reflex depression in the legs below the spinal injury. The spinal CT findings of Quencer *et al.* (1983) showed that 13 of their spinal cord cysts extended superiorly but only 1 extended inferiorly, indicating that the syrinx tended to ascend rather than to descend within the spinal cord. A change of the ascending sensory level was observed in the presence of postural changes in 3 of our patients. This can be explained by the fact that the syrinx, as demonstrated by gas myelography (Rossier *et al.*, 1983), can collapse and reexpand with postural changes. A suspended zone of intact sensation between the ascending sensory level and the level of the original spinal cord injury, which was rarely observed in the literature (Barnett and Jousse, 1973*a*; Watson, 1981), was seen in 5 of our patients. This does not indicate that the syrinx originated from a second and a higher lesion in the spinal cord as gas myelography (Rossier *et al.*, 1983) and autopsy findings (Oakley *et al.*, 1981) have shown that the syrinx usually arises and ascends from the site of the original spinal cord injury. Autonomic dysreflexia characterized by outbursts of paroxysmal hypertension, bradycardia, headaches, sweating and piloerection in response to stimuli from below the level of the spinal cord injury, especially from the bladder and bowel, is fairly common in patients with cervical and upper thoracic cord injury (Head and Riddoch, 1917). However, it is extraordinarily uncommon that this symptom of mass sympathetic discharge is the only presentation without sensory or motor changes in patients with syringomyelia. Neurological changes after metrizamide spinal CT or gas myelography, which occurred in a few of our patients and were usually transient, could be the result of the changes of the circulation of the fluid in the subarachnoid space and syrinx that occurred after some CSF was removed.

Electrophysiological Studies

Apart from fibrillation potentials and positive sharp waves which were infrequently seen, there was synchronous firing in involved muscles (Colinet *et al.*, 1965; Di Benedetto and Rossier, 1977), a pattern which is indicative of slowly progressive anterior horn cell dysfunction. Subjective sensory loss with intact sensory responses was typical (Fincham and Cape, 1968).

As F wave latencies were prolonged in all patients with a documented syrinx, it is postulated that this prolongation was the result of acute expansion of a syrinx with surrounding interstitial oedema. This interstitial oedema renders some anterior horn cells incapable of generating an efferent volley. When drainage of the cyst reduces this oedema the anterior horn cells become capable of functioning and reestablish their motor unit territories. McComas *et al.* (1975) and Rydevik and Nordborg (1980) have suggested that this type of motor neuron 'malaise' and return of function can exist at the anterior horn cell and peripheral nerve levels. The patient who failed to improve apparently suffered permanent partial loss of anterior horn cell function.

Intracavity and Cerebrospinal Fluids

Durward *et al.* (1982) and Quencer *et al.* (1983) stated that the syrinx fluid was similar to the CSF but they did not analyse the cyst fluid in their patients. Shannon *et al.* (1981) noted that, where chemical examination was performed, the protein level of the syrinx was like that of the accompanying CSF; however, in 2 of their cases, the cyst contained yellow fluid with a high protein content. Even though Barnett and Jousse (1973*a*) concluded that the fluid in the syringomyelic cavity resembled the CSF, in 3 of their 4 patients the protein content was higher in the cavity than in the cisternal CSF (Table 10). A review of the literature shows that the syrinx protein content was frequently elevated and higher than the cisternal CSF protein (Table 10), similar to our observations (Table 9).

While there is a normal range of CSF protein, the normal range for 'syringomyelic protein' has not been and probably cannot be determined. The origin of the syrinx fluid had been controversial. Gardner (1965), in studying communicating syringomyelia, examined the syrinx and lumbar CSF protein in 18 cases and found ranges between 0.16 and 0.90 g/l in the syrinx and between 0.15 and 0.59 g/l in the CSF. In 10 patients, the syrinx protein was below that in the lumbar CSF. Gardner and McMurry (1976) proposed that the syrinx protein originated from the ventricular system *via* the central canal; however, autopsy studies (Jensen and Reske-Nielsen, 1977; Oakley *et al.*, 1981) have shown that posttraumatic syringomyelia very seldom communicates with the central canal or the fourth ventricle. Although the syrinx may communicate with the subarachnoid space at the site of the original spinal fracture (McLean *et al.*, 1973), this is also very rare. Barnett *et al.* (1973) suggested that the syrinx protein was a secretion or transudate from the glial lining of the cyst. Ball and Dayan (1972) proposed that CSF might enter the cord *via* Virchow-Robin spaces which were found to be enlarged by Durward *et al.* (1982) in their autopsy examination of the spinal cord in 4 patients with syringomyelia. This theory is supported by the demonstration that metrizamide injected into the subarachnoid space may enter a syrinx cavity through the spinal cord (Seibert *et al.*, 1981). However, the elevated syrinx protein in our patients (Table 9) raises doubt about the hypothesis that the cystic fluid arises solely from the subarachnoid space.

Holmes (1915) presented pathological material showing a central area of degeneration within the spinal cord at sites adjacent to gunshot wounds extending up and down over several segments. He postulated that a syrinx resulted from pressures within the foci of degeneration. Other authors have suggested a similar mechanism following haemorrhage, necrosis, or a vascular contribution to the formation of the initial cavity (Nurick *et al.*, 1970; Barnett *et al.*, 1973). Jensen and Reske-Nielsen (1977) believed that their cases lent support to Holmes' original theory, in that their pathological findings suggested elevated intraparenchymal pressure without signs of haemorrhage or vascular compromise. W. H. Sweet (1984, personal communication) noted that there might be a striking increase in the total protein in Meckel's cave as compared with the posterior cranial fossa. He found that, in 4 patients, the protein content in Meckel's cave ranged from 0.16 to 0.60 g/l (mean 0.39) while the posterior fossa CSF protein ranged from 0.20 to 0.18 g/l (mean 0.12). He made an analogy to the difference of the CSF protein in the cisternal and lumbar subarachnoid space and he suggested that the higher protein content in Meckel's cave was the result of sluggish CSF circulation within the cave. The syrinx fluid with its elevated protein content in our patients was probably the result of degeneration of damaged cord tissue at or near the site of the original spinal injury in a usually enclosed space, in addition to the fluid entering the spinal cord *via* Virchow-Robin spaces.

Conservative Treatment

Barnett and Jousse (1973*b*) followed 6 patients treated conservatively. One patient was troubled by distressing pain and 1 by a neuropathic shoulder joint. Another had a serious disability including bilateral upper limb weakness and a neuropathic arthropathy of the left elbow; this patient's 19-year history, however, indicated that this condition might progress in an indolent manner. On the other hand, 2 of their patients definitely indicated a reduction of new symptoms: one had an increase in power of his hand and another had a remission of fasciculations in his tongue. Of the 4 patients of Quencer *et al.* (1983) who were not operated upon, 1 refused surgery, 2 had cysts that were thought to be too small (0.5 cm in length) to shunt, and in 1 patient the cyst was inadvertently punctured early in the operative procedure causing its collapse, after which the cyst could not be successfully catheterized. The authors made no statement about the follow-up of these patients. Vernon *et al.* (1982) noted that all patients who were not treated surgically gradually and invariably became worse.

Of the 19 patients treated conservatively, 6 had no observable neurological changes and in some of the others, the symptoms remained stable (Table 11) over a number of months or years. In general, the follow-up period of the patients who became worse was longer than the others whose condition or symptoms remained stable. Conceivably, a patient, if followed long enough, will eventually show some signs of progression. None of our patients had neurological remissions but none of them progressed to the state of 'quadriplegic helplessness' (Barnett and Jousse, 1973*a*) or severe disability.

Surgical Treatment

Peerless and Durward (1983) noted that drainage by needle aspiration with myelotomy alone or placement of a seton had poor results because of inability to maintain drainage of the syrinx. Barnett and Jousse (1973*b*) suggested that operative procedures such as plugging of the obex designed to deal with communicating or idiopathic syringomyelia, should not be performed in patients with posttraumatic syringomyelia which is not associated with a defect of the base of the skull or cerebellar tonsillar herniation. Nurick *et al.* (1970) reported the operative results of 2 patients with posttraumatic syringomyelia. A posterior fossa decompression and removal of C1 and C2 vertebral laminae followed by insertion into the upper end of the central canal of a small pledget of muscle was performed in their first patient. Postoperatively there was no immediate neurological change but the patient's condition slowly deteriorated over the following 6 years. Their second patient was treated with a small suboccipital decompression combined with removal of the arch of the atlas which was followed by occlusion of the opening to the central canal with a piece of suboccipital muscle; there was no change in his clinical findings six months after the operation.

Freeman and Wright (1953) showed that syrinx formation frequently followed experimental trauma to the spinal cord of cats and dogs and, after a series of controlled experiments, demonstrated that blunt myelotomy allowed the egress of necrotic material from the cord and reduced the likelihood of syrinx formation. Freeman (1959) extended his experimental findings and used syringostomy to treat a patient with posttraumatic syringomyelia and this patient had complete motor return after the operation. McLean *et al.* (1973) treated their patient by excizing part of the spinal cord and syrinx so that the cyst communicated widely with the subarachnoid space above and below the area of the old trauma; this patient had good sensory and motor return after the operation. Barnett and Jousse (1973*b*), who had good operative results in 7 patients, suggested that the surgical approach should be determined by the original disability. If the original lesion, excepting cervical injuries, led to a complete permanent disruption of spinal cord function, the best treatment for the syringomyelia was to drain the cavity at, or just above, the level of the original injury by complete transection of the cord at this level and by the insertion and fixation of a silastic tube into the cavity in the proximal stump of the resected spinal cord; however, Tator *et al.* (1982) have indicated that the adhesive arachnoiditis that may develop after a cordectomy may result in a worsening of symptoms. If the original injury led to a partial disruption of spinal cord function, the most beneficial approach would probably be at, and just above, the original injury site with the insertion of a silastic tube into the cavity and its fixation into the normal subarachnoid space above the level of injury (Barnett and Jousse, 1973*b*). Drainage of the syrinx with a permanent silastic shunt was also recommended by other authors (Williams *et al.*, 1981; Tator *et al.*, 1982; Quencer *et al.*, 1983) as this has been found to be a simple and predictable method with low morbidity (Shannon *et al.*, 1981). Tator *et al.* (1982) have also noted that silicone (silastic shunt material), unlike rubber and polyethylene, is less likely to cause arachnoiditis. A small Pudenz silastic ventricular catheter was used by Shannon *et al.* (1981), Tator *et al.* (1982) and Vernon *et al.* (1983) and a straight cordis ventricular catheter by Quencer *et al.* (1983); Peerless and Durward (1983) emphasized the placement of multiple side holes into the tubing to facilitate drainage. Laha *et al.* (1975), on the other hand, shunted the syrinx to the subarachnoid space with a silastic T tube in 3 patients, 2 of whom had significant postoperative improvement. Some of these operative procedures were carried out with the assistance of an operating microscope (Shannon *et al.*, 1981; Tator *et al.*, 1982; Quencer *et al.*, 1983) which facilitated preservation of the arachnoid membrane (Tator *et al.*, 1982). Williams *et al.* (1981)

recommended drainage into the peritoneum from the cavity as the fluid from the subarachnoid space could be forced back into the syrinx during a Valsalva manoeuvre. The results of Peerless and Durward (1983) indicated, however, a marginal benefit of the syringoperitoneal drain over syringosubarachnoid shunt. In addition, in canine kaolin-induced syringomyelia, Hall *et al.* (1980) showed that the pressure in the spinal subarachnoid space remained low, even when the intraventricular and intrasyringeal pressures were raised. Ellertsson and Greitz (1970) reported that the intramedullary spinal pressure exceeded the subarachnoid pressure in the patients who underwent percutaneous syrinx puncture. In the presence of such a pressure gradient, it is likely that drainage of the syrinx through the syringosubarachnoid shunt would be maintained provided that the shunt remained patent (Tator *et al.*, 1982). Some authors recommended the use of two shunts if the syrinx is multiloculated or large (Shannon *et al.*, 1981; Quencer *et al.*, 1983). Tator *et al.* (1982) chose to place the intramedullary catheter in the largest part of the cord while Peerless and Durward (1983) suggested that the drain should be placed in the lowermost extent of the syrinx.

With the exception of 1 patient in whom the T tube was functioning as a seton so as to allow the cyst fluid to drain into the subarachnoid space, the exclusive use of a syringosubarachnoid shunt allowed us to evaluate the efficacy of this technique only in the management of posttraumatic syringomyelia. The use of a T or K tube instead of a straight catheter permits drainage of the upper and lower parts of the cyst without suturing the shunt to the pia or arachnoid membrane. At the same time, the myelotomy was made wide enough to allow free passage of fluid around the shunt from the syrinx into the subarachnoid space. Unlike the technique of Tator *et al.* (1982), the arachnoid membrane in our patients was not closed under an operating microscope. In 3 of our patients whose posttraumatic myelopathy was located in the thoracic or thoracolumbar region of the spine, the shunt was placed in the widest part of the syrinx as shown by gas myelography. In other patients who had a fracture in the cervical or cervicothoracic spine, the syrinx was shunted with the end of the tubing cranially into the subarachnoid space, not only away from the site of trauma, but also well beyond the dural incisional site, where postoperative scarring occurs.

Barnett and Jousse (1973*b*) suggested that the decision for surgery for posttraumatic syringomyelia should be guided by several factors, namely the occurrence of pain, neuropathic joints and muscle weakness. Quencer *et al.* (1983), however, felt that a cyst-subarachnoid shunt is indicated if a cyst of significant size is present in an accessible location. All patients of Tator *et al.* (1982) who underwent the shunting procedure were showing significant progressive neurological deterioration preoperatively. The indications for surgical treatment in our patients were progressive muscle weakness and severe pain. Quencer *et al.* (1983) noted that the duration of the preoperative symptoms had no effect on the clinical outcome after operation. Tator *et al.* (1982) and Peerless and Durward (1983) observed that the shorter the duration of the presenting symptoms the better were the results following operation. Shannon *et al.* (1981) noted that the patients who initially sustained incomplete sensorimotor spinal cord damage had a better symptomatic response to surgery than those who had sustained a complete spinal cord lesion. Our observations show that almost all our patients who had pain ranging from 4 months to 6 years before surgery had major improvement after the shunting operation. With regard to motor deficits, our limited experience with only 1 patient shows that the shorter the preoperative duration of the symptom the better was the result after surgery. Unlike the findings of Shannon *et al.* (1981), most of our patients who underwent surgery had sustained a complete spinal cord injury and most of them had major improvement following surgery. Tator *et al.* (1982) did not notice any single symptom or sign or group of symptoms or signs to be of value for predicting the outcome of surgery. We agree with Shannon *et al.* (1981) and Vernon *et al.* (1983) that pain and motor deficits but not sensory deficits showed the most consistent response to surgical treatment. Our findings also show that very few patients had reflex return after operation (Table 12).

Transient and mild neurological deterioration can occur after operation. Early but permanent postoperative deterioration was seen in 2 of our patients. In 1 patient, the shunt was large and in the other, the syrinx was small. Several authors noted delayed recurrence of syringomyelic symptoms that required a second shunting operation (Barnett and Jousse, 1973*b*; Tator *et al.*, 1982; Peerless and Durward, 1983). A number of factors may be responsible for the late failure of a drainage procedure. The tube of the syringosubarachnoid shunt may have been placed in the subdural space instead of the subarachnoid space; it may have fallen out of the syrinx; or arachnoid scarring may have occluded its end (Peerless and Durward, 1983). Late drainage failure occurred in 3 of our patients. In 1 patient, the cyst was drained to the subarachnoid space by a T tube acting as a seton and in another, it was shunted with a silastic sponge-like post; adhesive arachnoiditis was the cause of late shunt failure in the third patient. Our experience with these patients shows the value of metrizamide spinal CT in the evaluation of recurrence of syringomyelic symptoms secondary to shunt obstruction (figs. 4, 5), in comparison to gas myelography which cannot show a collapsing or enlarged cord because it may be held to the arachnoid by postoperative adhesions. We agree with Peerless and Durward (1983) that attempts at early surgery to prevent progression may not be justified in patients who have symptoms that are relatively mild and stable and in patients who have radiological evidence of a small cyst.

Review of World Literature

Including our 30 cases, a total of 330 patients with posttraumatic syringomyelia have been described in the literature, including 152 patients who were operated upon and 15 autopsy cases (*see* Appendix). Only published cases of patients with traumatic closed injuries and clinical signs or symptoms of syringomyelia following spinal fracture, dislocation or both have been included in this review, excluding those cases reported in the previous personal communications. Wherever the same cases might have been described several times in different publications, the authors were personally contacted to obtain the necessary information (S. J. Peerless and R. M. Quencer, personal communications, 1984).

ACKNOWLEDGEMENT

We thank Mrs Patricia Bugbee for help with the statistical analysis.

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(*Received July 3, 1984. Revised October 18, 1984. Accepted October 27, 1984*)

APPENDIX

REVIEW OF THE WORLD LITERATURE UNTIL MAY 1, 1984

	Total cases	*Surgery*	*Autopsy*
Before 1920	3	0	1
After 1920	297	141	12+1*
Authors' series	30	11	1*
Total	330	152	15**

*Also included in the surgical series.

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THE ANATOMICAL BASIS OF SYMPTOMATIC HEMIDYSTONIA

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SUMMARY

Twenty-eight patients with focal (arm or leg) or hemidystonia due to tumour, arteriovenous malformation, infarction, haemorrhage or hemiatrophy are described. All had typical dystonic movements and/or postures, identical to those seen in idiopathic (primary) torsion dystonia. The site(s) of the lesion responsible, as defined by CT (computerized tomography) scan or pathological examination, was in the contralateral caudate nucleus, lentiform nucleus (particularly the putamen) or thalamus, or in a combination of these structures. Review of 13 other patients in the literature with hemidystonia and lesions defined by CT scan, and of 7 other patients with pathologically discrete lesions associated with hemidystonia, also indicated involvement of these structures. Dystonia may be due to abnormal input from thalamus to premotor cortex, due to lesions either of the thalamus itself, or of the striatum projecting by way of the globus pallidus to the thalamus.

INTRODUCTION

Torsion dystonia is characterized by inappropriate prolonged muscle contractions which forcefully distort the body into typical postures. Dystonia often initially occurs on action, but if more advanced it may be present at rest. Clinical and electrophysiological observations have shown that dystonic movements and postures are due to prolonged abnormal cocontraction of agonist and antagonist muscles, with abnormal recruitment ('overflow') of distant muscles during movement (Oppenheim, 1911; Foerster, 1921; Herz, 1944; Rothwell *et al.*, 1983). These characteristics distinguish torsion dystonia from other abnormal movements and from other abnormal postures such as decerebrate rigidity, spastic dystonia due to corticomotoneuron damage or the flexion dystonia of Parkinson's disease (Denny-Brown, 1968). The term athetosis, as introduced by Hammond in 1871, refers to dystonic movements of the fingers and toes.

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Torsion dystonia is generally considered to be a disease of the basal ganglia, but the evidence for this is still inconclusive. Disorders which may produce torsion dystonia, such as Wilson's and Leigh's diseases or carbon monoxide intoxication, are often not restricted pathologically to the basal ganglia. On the other hand, well-documented reports of patients with dystonia secondary to focal brain lesions are rare (Zeman and Whitlock, 1968; Narbona *et al.*, 1984). We have reviewed a series of 28 personally studied patients with focal dystonia or hemidystonia, in whom a localized brain lesion could be defined. A few of these patients, who showed special clinical features, have been reported before as separate cases (Brett *et al.*, 1981; Narbona *et al.*, 1984; Obeso *et al.*, 1984).

TABLE 1. CLINICAL DATA OF 28 PATIENTS WITH SYMPTOMATIC FOCAL OR HEMIDYSTONIA

Case	*Sex*	*Age at study (yrs)*	*Age at onset of dystonia (yrs)*	*Duration of dystonia (yrs)*	*Interval between onset of lesion and onset of dystonia*	*Site of onset of dystonia*	*Spread of dystonia*
1	F	13	12	1	0	L hand	None
2[a]	M	8	8	0.3	0	L hand	L arm and leg
3	M	38	37	0.5	0	Neck	None
4	F	44	43	1	0	Neck	None
5	F	10	9	1	0	R hand	R arm and leg
6	M	20	1	19	0	L arm and leg	None
7[b]	F	15	5	10	1 wk	R arm and leg	None
8	M	14	8	6	2 yrs	L hand	L arm and leg
9	F	23	4	19	0	L foot	None
10	F	76	68	8	2 mo.	R hand	None
11[c]	F	22	21	2	2 mo.	L arm and foot	None
12	F	64	62	2	6 mo	L hand	None
13	M	61	60	1	9 mo.	L arm and leg	None
14	F	32	22	10	0	L foot	L leg and arm
15	M	14	9	5	0	R arm	None
16	M	17	17	0.2	0	L hand	L arm
17	M	10	10	0.1	0	R hand	R arm and leg
18	M	36	7	29	4 yrs	R arm and leg	None
19	F	55	52	3	4 mo.	R hand and foot	None
20	M	55	51	4	6 mo.	R foot	None
21	F	53	50	2	1 yr	L limbs	None
22	F	60	51	9	3 yrs	L hand	L arm and leg
23	M	62	62	0.3	0	L hand	None
24	F	12	6	6	0	L arm	None
25	M	11	4	7	4 mo.	R arm and leg	None
26	F	17	1	16	1 yr	L arm and leg	None
27	F	21	17	4	14 yrs	R foot	R leg and arm
28	M	12	7	5	1 mo.	L arm and leg	None

[a] Previously reported by Narbona *et al* (1984) [b] Previously reported by Brett *et al.* (1981) [c] Previously reported by Obeso *et al.* (1984).

TABLE 2. TOPOGRAPHY AND AETIOLOGY OF DISCRETE LESIONS CAUSING FOCAL OR HEMIDYSTONIA IN 13 PATIENTS

Case	*Site of dystonia*	*Type of dystonia**	*Aetiology*	*Topography by CT scan*
1	L hand	SA	Glioma[a]	R lenticulocapsulothalamic
2	L hemidystonia	SAM	Astrocytoma[c]	R lentiform nucleus
3	Torticollis (head rotated to L)	SM	A-V malformation[c]	Head of R caudate nucleus
4	Torticollis (head rotated to L)	SM	A-V malformation[a]	Head of R caudate nucleus
5	R hemimyoclonic dystonia	AM	A-V malformation[b]	R lenticular nucleus
6	L hemidystonia	SAM	Infarction[a]	Head of R caudate nucleus
7	R hemidystonia	SAM	Traumatic infarction[a]	L lentiform nucleus
8	L hemidystonia	SAM	Traumatic infarction[b]	R capsulolenticular
9	L foot	SAM	Infarction[a]	R capsulolenticular
10	R hand	SAM	Infarction[a]	L posterolateral thalamus
11	L hand	AM	Infarction[b]	R posterolateral thalamus
12	L hand	SAM	Infarction[a]	R posterolateral thalamus
13	L hemidystonia	SAM	Haemorrhage[a]	R posterolateral thalamus

* Type of dystonia. S = spontaneous dystonia A = intensified by action. M = mobile dystonic spasms causing repetitive dystonic postures. F = fixed, present at rest and action, but not intensified by action; no mobile dystonic spasms.

[a] Diagnosis established by CT scan. [b] Diagnosis established by CT scan and angiography. [c] Diagnosis established by histology.

THE PATIENTS

The 28 patients with focal dystonia or hemidystonia secondary to a localized brain lesion included in this study were selected from a larger group of patients with symptomatic dystonia. Inclusion criteria were that the clinical characteristics of the focal dystonia or hemidystonia were identical to dystonic movements and postures present in patients with idiopathic torsion dystonia. The topography and aetiology of the lesions were defined by CT scan studies in all patients. Postmortem pathological study was carried out in 1 patient and biopsy of the lesion was undertaken in 4 cases.

The general clinical data of the 28 patients are summarized in Table 1. The pathology and CT scan localization of their lesions are shown in Tables 2 and 3. From the point of view of clinicopathological correlation we have separated our patients into two groups: (1) patients with dystonia secondary to a relatively small discrete brain lesion (Table 2); (2) patients with dystonia secondary to a large lesion affecting several brain structures (Table 3). Within each group the patients have been ordered according to the pathological nature of their lesion. Representative cases are illustrated at length.

TABLE 3 TOPOGRAPHY AND AETIOLOGY OF LARGE LESIONS CAUSING FOCAL OR HEMIDYSTONIA IN 15 PATIENTS

Case	*Site of dystonia*	*Type of dystonia**	*Aetiology*	*Topography by CT scan*
14	L foot	A	Astrocytoma[c]	R frontocaudate
15	R arm	SAM	Glioma[b]	L lenticulothalamocaudate
16	L arm	SAM	Astrocytoma[c]	R lenticulothalamocaudate
17	R hemidystonia	AM	A-V malformation[c]	L frontolenticulothalamocaudate
18	R hemidystonia	SAM	Traumatic infarction[a]	L lenticulocapsulocaudate
19	R hemidystonia	SA	Thrombotic infarction[a]	L lenticulocapsulocaudate
20	R foot	SA	Thrombotic infarction[a]	L lenticulocapsulocaudate
21	L hemidystonia	SA	Embolic infarction[a]	R lenticulocapsulocaudate
22	L hemidystonia	SAM	Thrombotic infarction[a]	R lenticulocapsulocaudate
23	L hand	SAM	Embolic infarction[b]	R parietothalamic
24	L hemidystonia	SAM	Tuberculous meningitis	R hemiatrophy, R frontocaudate infarction
25	R hemidystonia	SAM	Birth anoxia[a]	L hemiatrophy
26	L hemidystonia	SAM	Birth anoxia[a]	R hemiatrophy
27	R hemimyoclonic dystonia	SAM	Infantile epilepsy and hemiplegia[a]	L hemiatrophy
28	L hemidystonia	SAM	Infantile epilepsy and hemiplegia[a]	R hemiatrophy

* Type of dystonia: abbreviations as in Table 2. [a] Diagnosis established by CT scan. [b] Diagnosis established by CT scan and angiography. [c] Diagnosis established by histology.

CASE HISTORIES

Discrete Lesions

Focal or Hemidystonia Secondary to Restricted Basal Ganglia Tumour

Case 1. A 13-year-old girl was the product of a normal pregnancy and birth, and psychomotor development was normal. There was no family history of neurological disease. Involuntary movements affecting her left hand started insidiously around April 1978. She did not describe weakness, sensory loss or paresthesiae. Examination in May 1979 revealed a marked dystonic posture of the left upper limb at rest. This consisted of extension of the wrist and first metacarpophalangeal joints with flexion of the fingers and abduction of the thumb (fig. 1A, B). There were no superimposed dystonic spasms, but the abnormal posture was greatly aggravated by actions such as holding the arm outstretched or writing. Dystonia interfered with tests of coordination of the left arm. Tone in the left hand, wrist and forearm was increased in all directions of passive movement throughout the range of movement. There was no tremor. Power was normal as were the tendon reflexes, and both plantar responses were flexor. Sensory examination, speech, the cranial nerves and intelligence were all normal. CT brain scan showed a lesion of the right lentiform nucleus, intruding into the right ventrolateral thalamic nuclei, which enhanced after contrast injection (fig. 1C); it distorted the third ventricle, and higher CT cuts indicated mild hydrocephalus. A right carotid angiogram ruled out an arteriovenous malformation. The CT scan appearance suggested a glioma. Accordingly, the ventricles were shunted and the patient received radiotherapy directed to the lesion (50 Gy per day over eight weeks). Subsequently, the dystonia of the left arm gradually improved and the CT scan lesion resolved. When she was last examined in December 1983, the dystonia of the left hand had almost disappeared (fig. 1D). The patient was then capable of carrying out all kinds of manual tasks, such as typing and writing.

Case 2. This patient has been reported in detail previously by Narbona *et al.* (1984). The present description is therefore a summary. An 8-year-old boy was first seen in August 1979 with a four-month history of abnormal postures and involuntary movements of the left limbs. His past medical and family history was unremarkable. Symptoms had begun with the left hand adopting unwanted postures on action. This progressed to involve all manual activity. Three months after the onset of symptoms in the left hand, the left foot also became affected, showing plantar flexion and inversion on walking. Examination revealed a dystonic posture of the left arm on action, with the wrist going into ulnar deviation and slight flexion, and the fingers extending. The outstretched left arm also adopted a similar posture, with additional excessive pronation. At rest, the left foot was inverted and plantar flexed, with a tendency for the left hallux to extend spontaneously. Power, sensation and tendon reflexes were normal in the affected limbs. The rest of the neurological examination was normal. A CT scan in September 1979 revealed a high density lesion with an area of low attenuation within its anterior extent, which enhanced with contrast, in the right lentiform nucleus; it did not cause displacement. Six

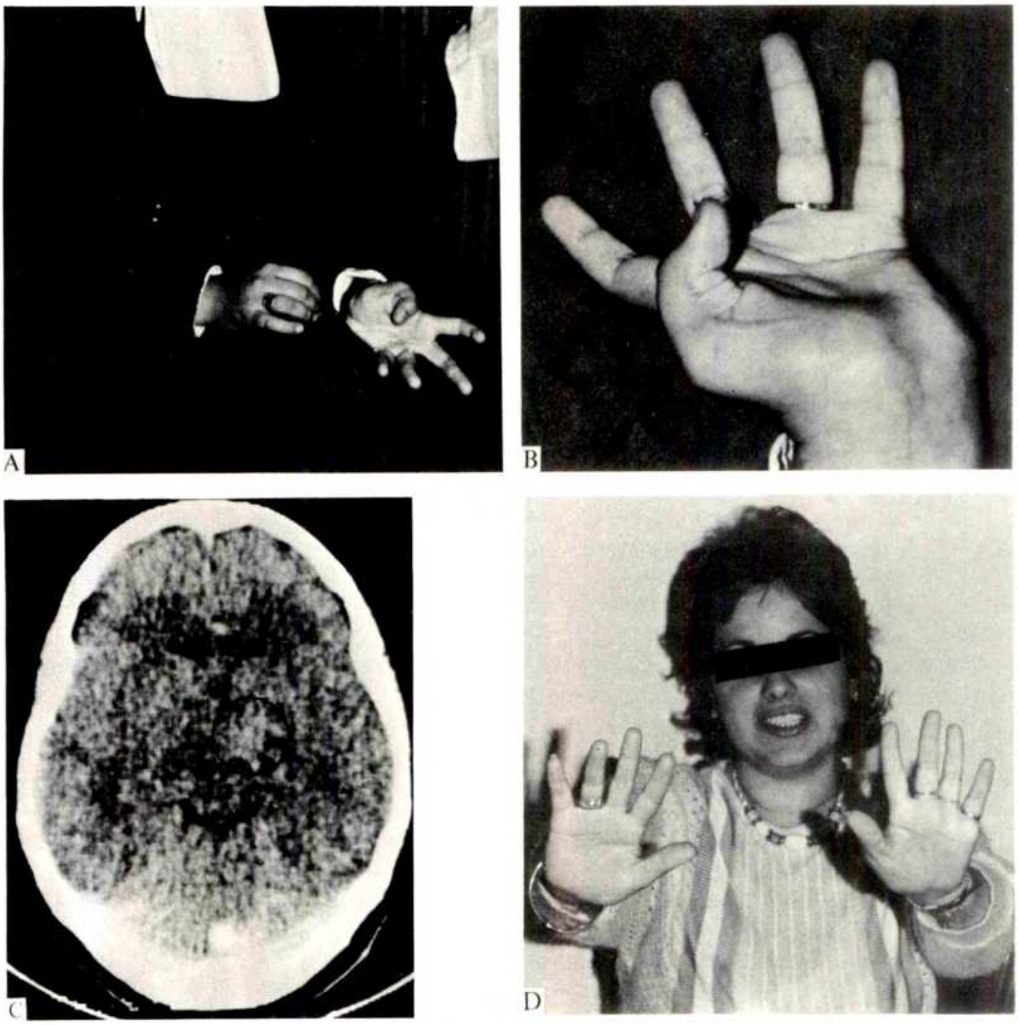

FIG. 1. *Case 1.* A and B show dystonic posture of left hand. C, CT scan with contrast showing high density lesion in region of right lenticular nucleus, internal capsule and thalamus (enclosed in circle). D, same patient four years later after treatment with radiotherapy.

months after the onset of the hemidystonia, the left arm became clumsier and walking was very difficult. He had developed pyramidal signs in the form of slight weakness of extensor muscles of the foot, exaggerated tendon reflexes in the left leg and arm, and a left extensor plantar response. The CT scan appearance suggested a glioma. He was treated with dexamethasone (4 mg daily) and radiotherapy (20 sessions of 5 Gy each) directed towards the lesion. The left-sided weakness resolved, but twelve months later the hemidystonia worsened and the left hemiplegia recurred. Intrathecal methothexate was commenced but four days later he died of a massive gastric haemorrhage. Necropsy was performed four hours after death. The brain weighed 1530 g and looked normal in external appearance. After formalin fixation, serial coronal slices revealed slight hydrocephalus and a tumour predominantly in the inferolateral segments of the left putamen and adjacent external segment of the globus pallidus. Histology showed the features of a grade II astrocytoma, with moderate hypercellularity and only a few undifferentiated cells. The tumour was confined histologically within the basal ganglia to the putamen and external segment of the globus pallidus, with slight extension inferiorly into the hypothalamus and anterior commissure (fig. 2).

Anteriovenous Malformation of the Head of the Caudate Nucleus Causing Torticollis

Case 3. A 38-year-old man, without previous history of neurological or systemic disease, was admitted in March 1980 for investigation and treatment of torticollis. He had been the product of a normal pregnancy and delivery, and psychomotor development was normal. There was no history of drug intake. The torticollis started gradually with jerky movements six months before admission, increasing progressively to produce permanent rotation of the head to the left. Neurological and general physical examination was normal, except for the presence of spasmodic torticollis with the chin directed to the left. In addition to the abnormal posture, there were spasms jerking the chin to the left. There also was slight rotation of the trunk to the right (fig. 3A, B). A CT scan showed a partially calcified mass in the head of the right caudate nucleus, which enhanced after contrast injection (fig. 3C). The right lateral ventricle also was slightly dilated. A right carotid angiogram did not reveal any abnormality of the arterial circulation, but the caudate and septal veins were abnormally increased in size. Surgical resection was attempted. The pathological report of the excised specimen was consistent with a partially calcified angioma, probably a venous angioma (fig. 3E). Following the operation the

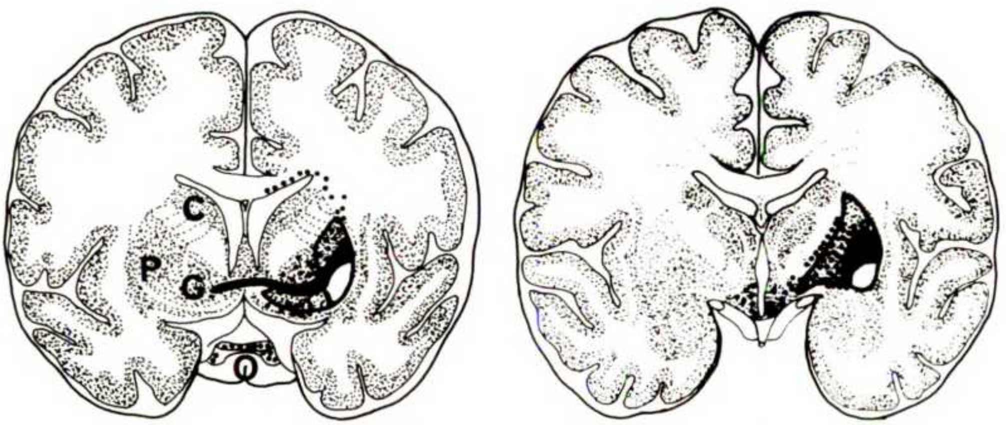

FIG. 2. *Case 2.* Reconstruction of distribution of tumour at the level of the anterior commissure based on pathological examination of serial brain slices. The white area in the inferolateral portion of the putamen (P) was the zone of cystic necrosis. The solid black area indicates solid tumour, extending into the anterior commissure. The black dots indicate perivascular infiltration into the globus pallidus (G), optic chiasma (O) and white matter around the lateral margin of the caudate nucleus (C) and corpus callosum.

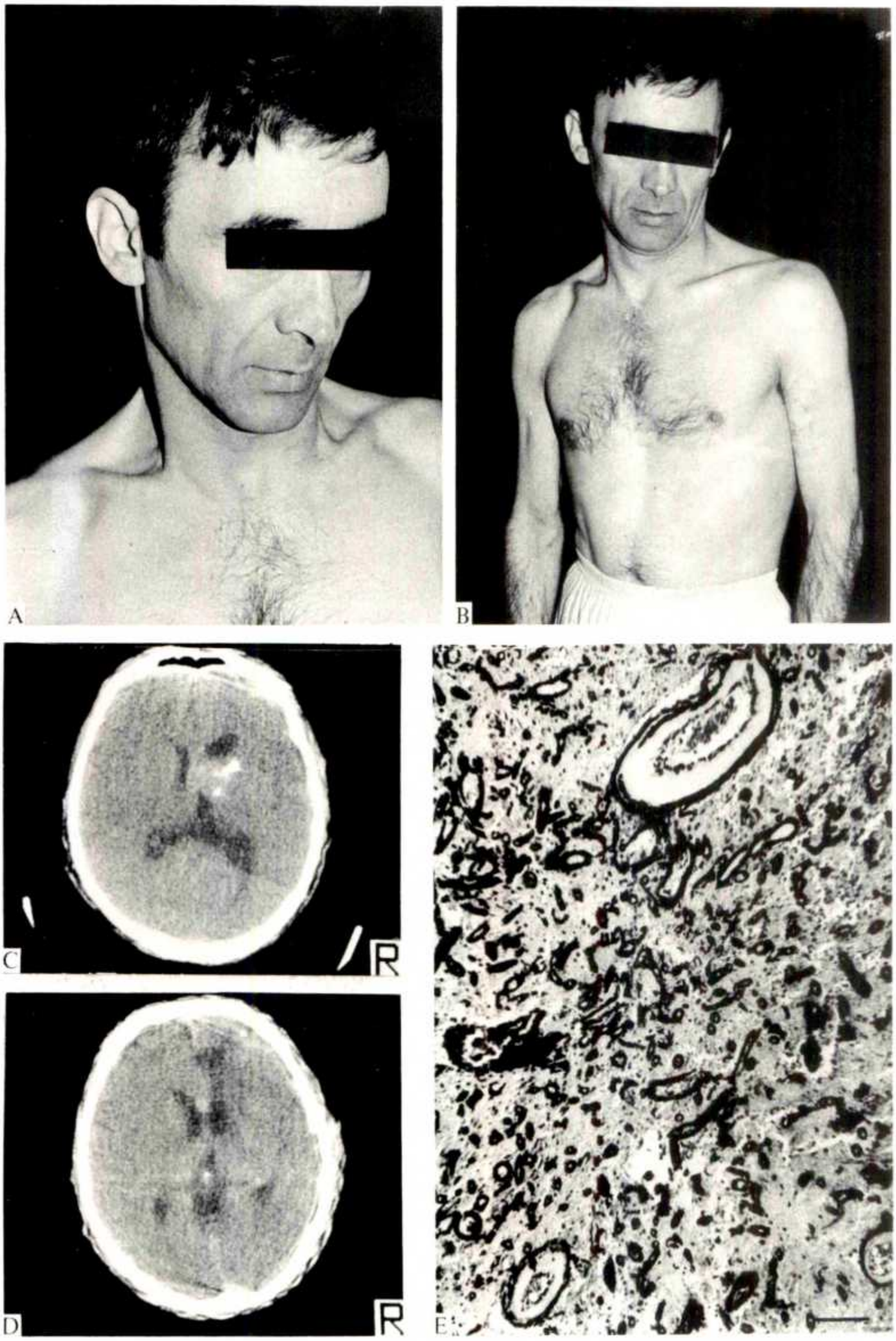

FIG. 3. *Case 3.* A and B show the patient's torticollis. C and D show CT scans before (C) and after surgery (D). E shows histology of the partially calcified angiomatous lesion removed at operation. Haematoxylin and eosin. Horizontal bar = 250 μm.

patient had an anomic aphasia, was apathetic and disorientated. The torticollis disappeared for two or three weeks, but returned thereafter. A repeat CT scan showed a small part of the malformation remaining attached to the anterior part of the septum pellucidum and a low density area in the right frontal lobe (fig. 3D). Four months later the patient was admitted in coma with severe neck stiffness. Lumbar puncture revealed fresh blood. He died within a few hours from an intraventricular haemorrhage. Necropsy was not allowed.

Focal Lesion of the Right Lentiform Nucleus of Posttraumatic Origin Causing Left Hemidystonia

Case 8. This boy was quite healthy until the age of 6 years when he sustained a mild head injury while playing football in 1972. Pregnancy, delivery and early development had been normal. His parents were healthy and two sibs were normal. The head injury itself was not severe, consisting only of a clash of heads, but he fell to the ground, conscious but with a weak left arm and leg. There was no headache or speech disturbance. The left leg recovered over the next month, leaving him with a mild hemiplegic gait, but the left arm did not regain much use and remained paretic. Skull x-rays, EEG, static and functional isotope brain scans and a right carotid arteriogram were all normal. He remained well until about 1977, when he gradually began to develop writhing dystonic movement of the left arm and leg. These abnormal movements gradually became worse. In 1977 he began to experience rare left-sided focal sensorimotor seizures lasting a few seconds, sometimes followed by weakness of the left limbs for 1–2 h.

On examination in 1980, at the age of 14 years, he was an intelligent lad with a very mild left hemiparesis affecting face, arm and leg, with increased tendon reflexes in the left limbs, and an extensor left plantar response. There was no sensory abnormality. The left hand was held flexed at the wrist and extended at the fingers and exhibited continuous dystonic spasms of pronation and excessive flexion of the wrist. The left arm hyperpronated when outstretched and dystonic spasms were intensified by any attempted use of the arm. The left foot also exhibited spasms of plantar flexion and inversion,

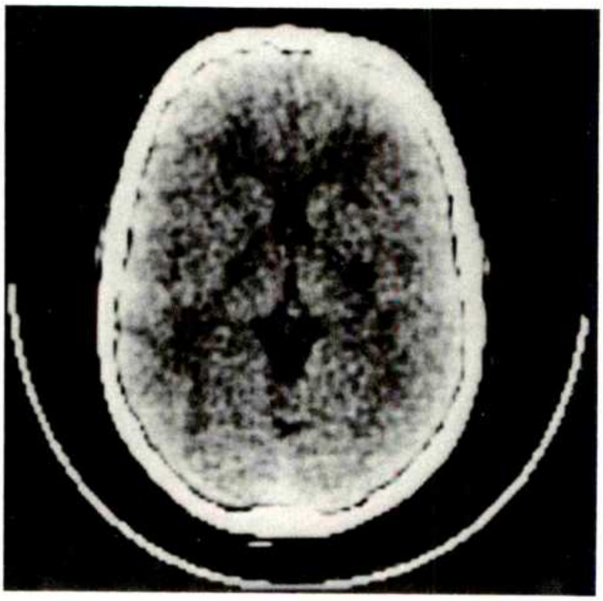

FIG. 4. *Case 8.* CT scan without contrast showing low density lesion in right lentiform nucleus. Clinical examination also indicated involvement of the internal capsule.

especially when walking. Investigation in 1980 revealed normal skull x-rays, serum copper and caeruloplasmin, liver function and plasma proteins and electrolytes, normal CSF cell count, protein and syphilitic serology. An EEG showed an asymmetry of the alpha rhythym and an excess of slow wave activity over the left hemisphere, but no evidence of spikes or sharp waves. A CT scan revealed an area of low attenuation adjacent to the right internal capsule in the lentiform nucleus (fig. 4).

Focal Thalamic Infarction Causing Hand Dystonia

Case 10. A 67-year-old lady with a past history of hypertension (180/120) suffered a stroke in January 1976. Her right upper limb was paralysed and there was a complete right hemisensory loss. Visual fields, speech, mentation and eye movements were normal. An isotopic brain scan indicated an abnormal area of uptake in the left thalamus. She recovered full motor power, but two-point sensory discrimination remained abnormal. In addition, spontaneous pain in the right limbs developed, which was intensified by tactile stimulation. In 1978, the pain and sensory loss had subsided considerably. She then started to develop an abnormal posture of the right hand. Examination at that time revealed a dystonic posture of the right hand (fig. 5A, B) with flexion of the metacarpophalangeal joints and separation and extension of the fingers. This dystonic posture was exacerbated by voluntary movement

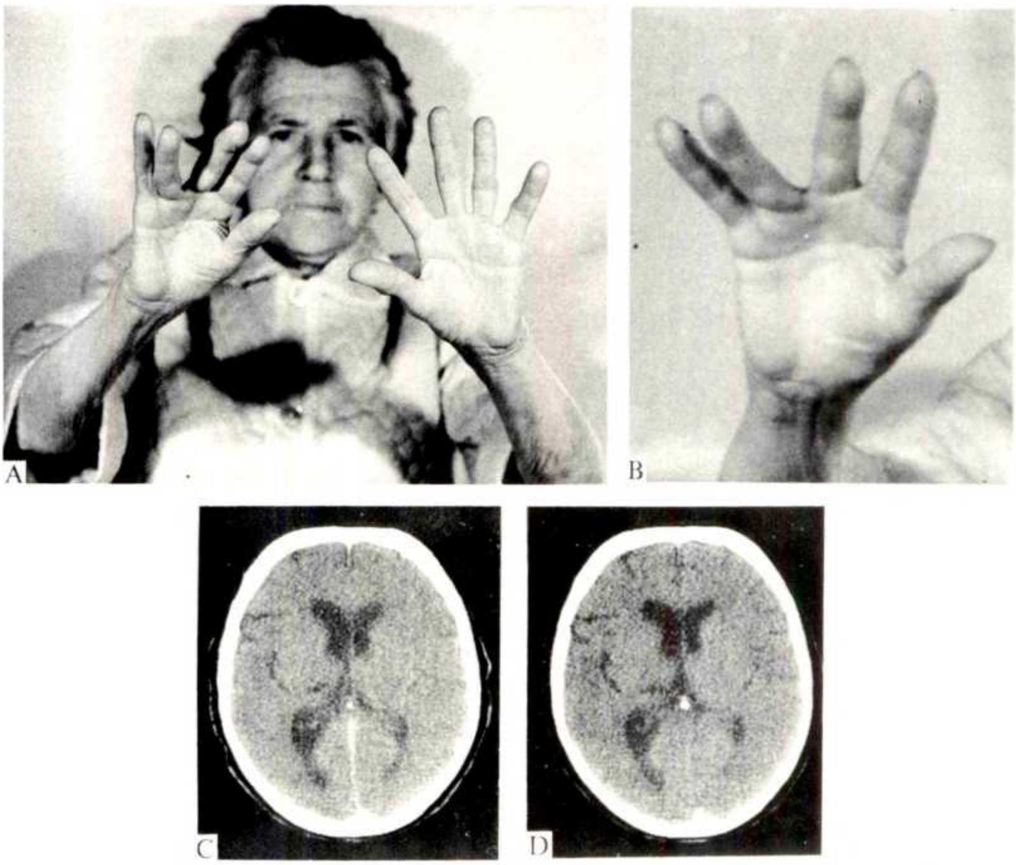

FIG. 5. *Case 10*. A and B show dystonic posture of right hand. C and D are CT scans, C without and D with contrast, showing low density lesion in left posterolateral thalamus.

of the right hand. Motor power in the right limbs was normal, as were the tendon reflexes; the plantar responses were flexor. Position sense and vibration sense were normal, but pain and temperature threshold was increased in the right arm. Coordination of the right limbs was normal. A CT brain scan showed a small low density lesion affecting the left posterolateral thalamus (fig. 5C, D).

Case 11. This patient has been described in detail previously by Obeso *et al.* (1984). A brief summary is included here. A 22-year-old pregnant woman developed a left hemiplegia in November 1981 during an episode of migraine lateralized to the right side of her head. The initial neurological examination revealed complete left hemiplegia and sensory loss. Visual fields were normal. Detailed cardiovascular examinations, including ECG and echocardiography were normal. A CT brain scan showed a large area of low density affecting the right posterolateral thalamus, internal capsule and lentiform nucleus within a week of the episode. The patient recovered motor power almost completely, and only a minimal hypoaesthesia of the finger tips could be detected on sensory examination. A few weeks later she developed spontaneous pain and a feeling of burning in the left arm. The pain was also provoked by tactile stimulation of the affected limb. Over the following two months mobility returned to normal and the abnormal sensation disappeared. However, she developed progressive difficulty in controlling the left arm and a tendency of the left foot to twist inwards on walking. Ten months after the acute

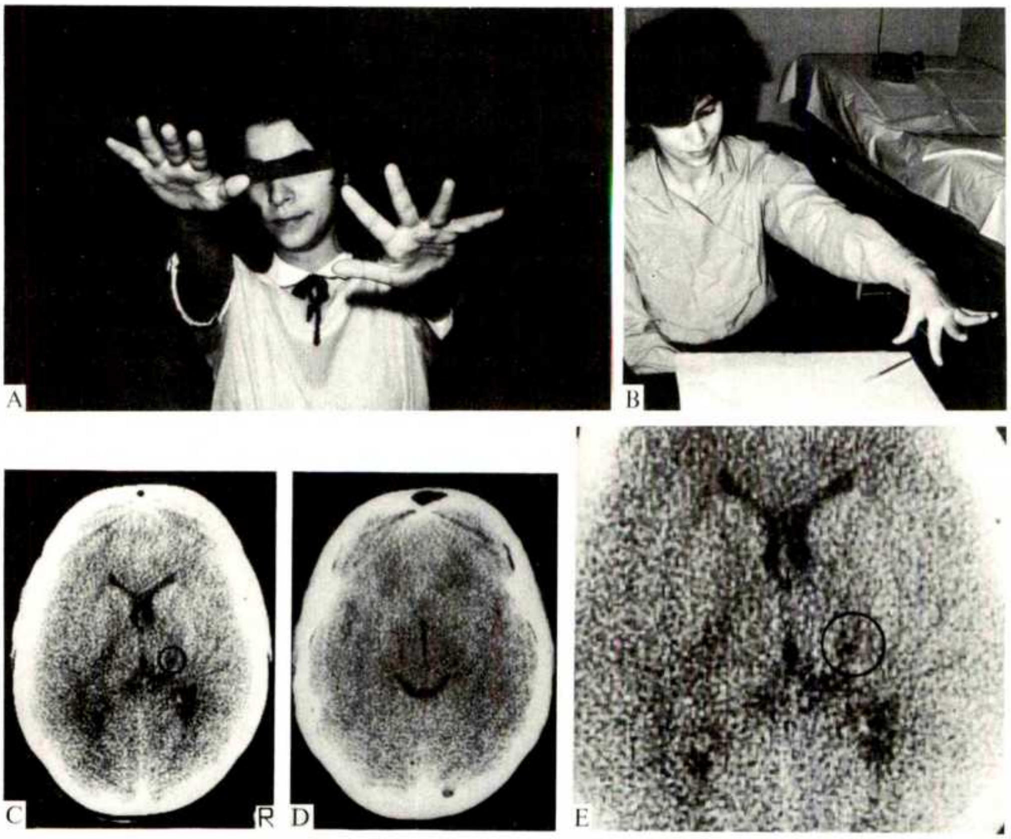

FIG. 6. *Case 11.* A and B show dystonic left hand and arm. C, D and E are CT scans without contrast showing a low-density lesion in right posterolateral thalamus (ringed).

episode, examination showed left arm dystonia on action of distal distribution (fig. 6A, B), and a coarse postural and kinetic tremor, of proximal distribution. A further CT brain scan showed a small area of low density in the right posterolateral thalamic nuclei (fig. 6C–E).

Large Lesions

Right Frontal Lobe Glioma Invading the Basal Ganglia Causing Left Foot Dystonia

Case 14. A 32-year-old nurse presented with her first major seizure in 1971. Occasional grand mal seizures, without focal onset or aftermath, continued until the age of 35 years, when she began to develop a progressive left hemiplegia, beginning in the leg. A CT brain scan at that time revealed a large area of low attenuation in the right frontotemporal region extending down to the midline, with compression of the anterior horn and body of the right lateral ventricle. There was no enhancement with contrast. Management was complicated by travel, but eventually she was admitted for surgical exploration in 1977, at the age of 36 years.

On examination then, she walked with a bizarre dystonic posture of the left leg and arm, and had a moderate left hemiparesis. The remainder of the neurological examination was normal.

A right frontal lobectomy was performed. Histology revealed a grade I astrocytoma. Thereafter she gradually improved, so that by 1979 her walking had returned to normal and she returned to work as a nurse. No further grand mal seizures occurred while on carbamazepine and phenobarbitone, although she did have occasional absence attacks. In 1981, however, the dystonic gait rapidly recurred over a matter of three weeks.

Re-examination then revealed an abnormality of gait similar to that seen previously. When attempting to walk forwards, the left knee would bend and the whole body would tilt to the left and sag towards the floor. She could run forwards without difficulty and could walk backwards normally. Also, she could hop on the affected leg without difficulty. Examination of the left leg on the bed revealed no change in tone and no weakness; the tendon jerks in the legs were normal and the plantar responses were flexor. There was no sensory loss in the legs. However, there was a mild left faciobrachial weakness of cortical distribution affecting both flexors and extensors and most marked proximally. The tendon jerks in the arms were normal and there was no sensory loss. The cranial nerves were normal.

A repeat CT scan showed recurrence of the tumour, with a large low density lesion occupying the right frontal and temporal regions, and extending posteriorly and across the midline to involve the caudate nucleus, compressing and displacing the right frontal horn of the lateral ventricle. The lesion showed patchy enhancement with contrast.

Left Hemidystonia Secondary to Right Lenticulocapsulocaudate Infarction

Case 22. This 60-year-old woman suffered a stroke in 1972 resulting in a complete left hemiplegia, without disturbance of speech or vision. The weakness improved over the next few months and she could walk and use her left hand almost normally. In 1975, the left upper limb began to tighten with the fingers flexing into the palm, the arm abducted to the side and the elbow flexing. This abnormal posture increased over the next five years. Forearm pains produced by the muscle spasms were an additional complication.

On examination in 1984, the left arm was held flexed at the elbow and abducted at the shoulder. Most of the time the fingers were flexed into the palm, but she was able to extend the first two fingers voluntarily. The other fingers could also be extended for a short period of time, but adopted a dystonic flexor posture as soon as any voluntary movement of the left upper limb was attempted. The left leg also went into forceful extension at the knee with ankle inversion upon action. In addition, the leg extended involuntarily when she was sitting or when she tried to execute any other motor task. There was mild pyramidal weakness in the left arm, but power in the legs was normal. The tendon jerks were difficult to elicit in the left arm because of the marked dystonic posture, but those in the leg were normal and symmetrical. The plantar responses were flexor. Sensation, speech, vision, the cranial nerves and

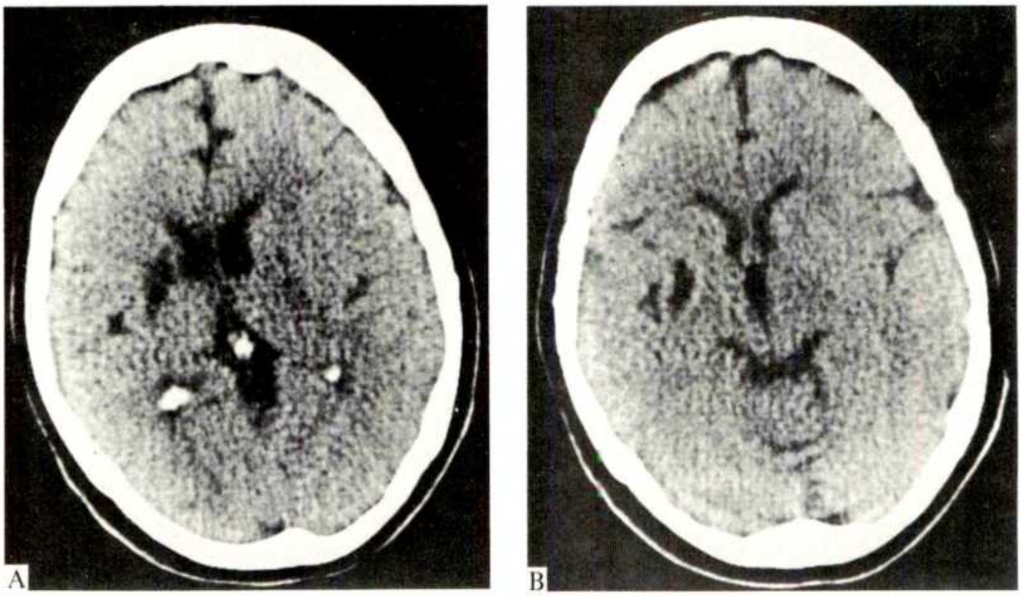

FIG. 7. *Case 22.* A and B are CT scans without contrast showing low density lesion in right (note different presentations of sides from previous scans) caudate nucleus and lentiform nucleus. Clinical examination also indicated involvement of the internal capsule.

intellect were normal. A CT brain scan showed a large infarct involving the right putamen (anterior third) and caudate nucleus (fig. 7A, B).

Left Hand Dystonia and Arm Action Tremor Secondary to Right Parietothalamic Infarction

Case 23. A 62-year-old man admitted in June 1983 in acute cardiac failure secondary to left ventricular infarction with partial rupture of the ventricular wall. An emergency cardiac repair was carried out, the patient recovering normal haemodynamic function over the next few days. Two weeks after admission he started to complain of clumsiness of the left hand, particularly when undertaking fine manipulative motor tasks. This progressed to frank incoordination of the left arm. Examination showed coarse postural and kinetic tremor of the left upper limb affecting mainly proximal muscles. There was an abnormal flexed posture of the third to fifth fingers with slight ulnar deviation of the wrist (fig. 8A). There was a minimal paresis of the small hand muscles and of the long finger extensors of the affected limb, but no sensory loss. Visual fields, speech, the tendon reflexes and plantar responses were normal. Three days later the tremor suddenly stopped. Examination then showed profound sensory loss for all modalities in the left upper limb and severe hypoaesthesia in the left side of the face and left leg. The dystonic hand remained unchanged. A CT brain scan showed a large parietal infarct extending deeply into the thalamocortical projections and probably also affecting the posterior thalamic nuclei (fig. 8B–E). Over the following weeks the dystonia disappeared completely and the sensory loss improved, but severe spontaneous pain of the left upper limb supervened. He was treated with carbamazepine (1200 mg/day) with partial improvement.

Right Hemiatrophy and Frontocaudate Infarction Causing Left Hemidystonia

Case 24. A 3-year-old Indian girl developed tuberculous meningitis, which was treated briefly for four months with antituberculous drugs. At the age of 6 years she again developed tuberculous

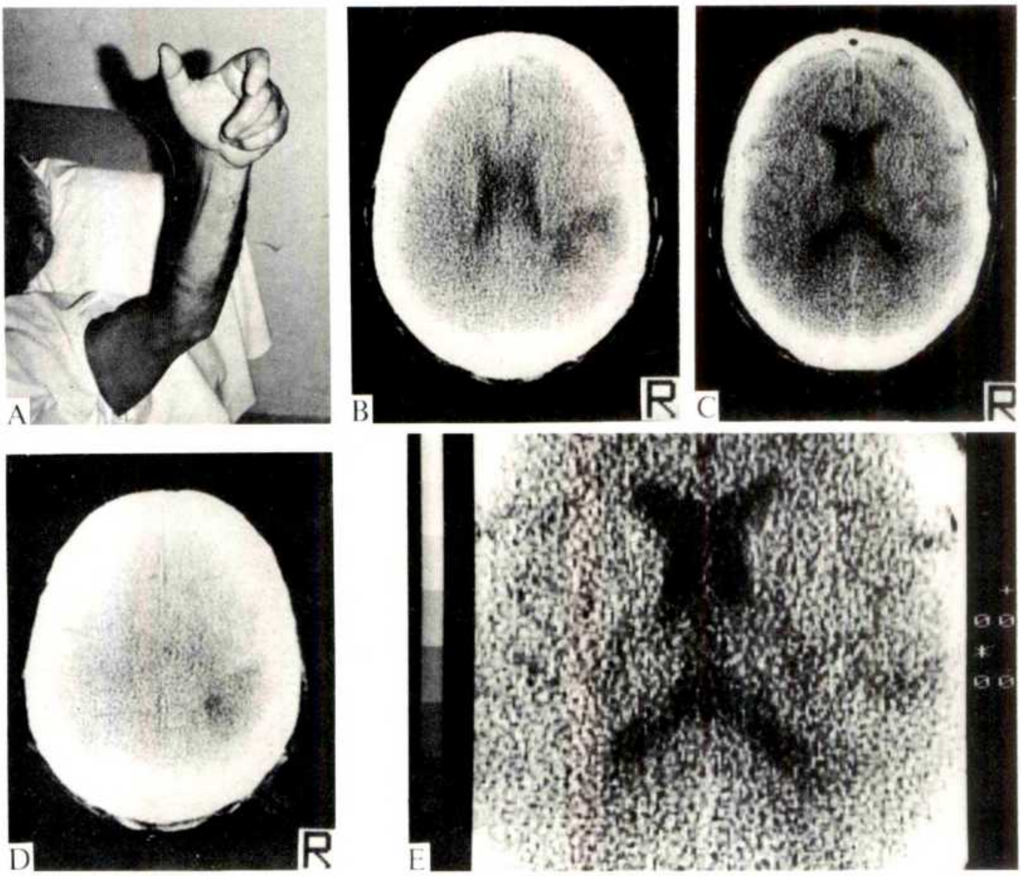

FIG. 8. *Case 23*. A shows dystonic left hand. B, C, D and E are CT scans without contrast showing large low density lesion in right parietothalamic region.

meningitis during which she suddenly developed a left hemiparesis. A right carotid arteriogram showed evidence of an arteritis. Again she was treated briefly with antituberculous drugs, but suffered a relapse of her meningitis. She developed bilateral papilloedema, stupor, and continuous dystonic movements of the left arm, with intermittent similar movements of the left leg. Investigation then revealed the CSF to be under increased pressure, and to contain 370 white cells (52 % polymorphs and 48 % mononuclear cells), protein 1.25 g/l, sugar 2.9 mmol/l (blood sugar 7.8 mmol/l); acid fast bacilli were seen with fluorescent staining. She was treated with streptomycin, isoniazid, rifampicin and dexamethasone, as well as ventricular drainage for hydrocephalus. Eventually she recovered, but was left with a left hemiparesis with dystonic movements.

On review at the age of 12 years, she was alert and intelligent, but disabled by dystonic posturing of the left limbs. The left arm, which was more affected than the leg, tended to abduct, spontaneously and suddenly, sufficiently strongly to strike those nearby. On attempting to hold the left arm outstretched, it adopted a typical dystonic posture with hyperpronation, and flexion of wrist with extended fingers. On walking, the left leg extended with plantar flexion and inversion of the foot. Power was normal, but the tendon reflexes on the left were brisk and the left plantar response was extensor; there was no sensory deficit. A CT brain scan at that time showed hemiatrophy of the right side of the cerebrum, with enlargement of the ventricles, particularly of the right frontal horn. There was an area of low attenuation deep in the right frontal lobe adjacent to the anterior horn, and the basal structures of the floor of the right ventricle were grossly atrophied.

Left Hemiatrophy Secondary to Anoxia at Birth. Right Hemidystonia

Case 25. A right hemiparesis was first found when this lad was aged 6 months, at which time he preferentially used the left hand. Pregnancy, delivery, and early development until then were normal. His unrelated parents were in good health, and there was no family history of any movement disorder. By the age of 4 years it was evident that the right arm was spastic with the wrist pronated and the fingers extended. In addition, there was mild spasticity of the right leg, and the plantar responses were extensor bilaterally. Schooling proved difficult and an IQ estimation at the age of 8 years gave a verbal score of 80 and a performance score of 90. From the age of about 4 years onwards it was noticed that the right arm would adopt a bizarre dystonic posture on any attempted action.

On examination at the age of 11 years the striking abnormality was the dystonia of the right arm. At the slightest attempt to move the arm, it would abduct at the shoulder, flex at the elbow, pronate at the forearm, flex at the wrist and extend at the fingers. The arm was useless and he had to employ the left hand for everything. The cranial nerves were normal, but the right foot was slightly plantar-flexed and inverted. The tendon reflexes were brisk on the right, and the right plantar response was extensor. A CT scan undertaken at the age of 11 years revealed a well-circumscribed atrophic area containing CSF which appeared to connect inferiorly with the junction of the insula and the sylvian fissure; it extended upwards to replace the temporal operculum and stretched down to the level of the left frontal horn. The left hemisphere as a whole was slightly smaller than the right, the left ventricular system was enlarged, and there was some atrophy of the cortical gyri on the left. The picture was of left hemiatrophy, with a discrete focal area of brain loss.

DISCUSSION

Focal brain lesions occasionally produce typical focal or hemidystonia. The lesions described here were tumours, arteriovenous malformations, infarcts (post-traumatic, thrombotic or embolic), or haemorrhages. Such lesions involved a variety of cerebral regions including the thalamus, caudate nucleus, lentiform nucleus (putamen and globus pallidus), internal capsule and cortex. Sometimes generalized hemiatrophy, also involving these structures, was found.

All these patients had typical features of torsion dystonia when examined. Thus 24 of the 28 patients exhibited spontaneous dystonic movements or postures at rest, 26 had dystonic movements or postures on action, and 23 had mobile dystonic spasms either at rest and/or on action. Some of these patients had slow writhing movements, others had more myoclonic jerks as described in myoclonic dystonia (Obeso *et al.*, 1983).

Focal or hemidystonia was the only neurological abnormality in many of these patients. However, 15 of the 28 cases had a history of a previous hemiparesis or hemiplegia due to cerebral infarction. These patients therefore had posthemiplegic dystonia. In 13 of these 15 patients the dystonia appeared after a delay of between two months to four years, often as the hemiparesis resolved. Hammond (1871) is credited with the first description of posthemiplegic 'athetosis' and Gowers (1886) clearly recognized the sequence of events occurring in those who developed delayed onset posthemiplegic dystonia. Indeed, Gowers (1886) also drew attention to the variety of abnormal movements and postures that might follow a stroke, varying from quick clonic spasms, to slow mobile spasms and tonic immobile spasms. All these are included in what now is termed dystonia; they are identical to the movements and postures seen in patients with idiopathic (primary) torsion dystonia, whether inherited or sporadic. Why there should be a delay in the appearance of dystonia following a stroke is not certain. The hemiplegia itself may prevent the appearance of dystonia, but this cannot be the only explanation. Some patients in this series (e.g. Case 8) had only the mildest hemiparesis yet dystonia did not appear for two years after a head injury associated with a lenticular infarct. In Case 7, a similar posttraumatic infarct in the lentiform nucleus was accompanied by virtually no pyramidal deficit, yet dystonia appeared a week later and became progressively worse over the next two years (Brett *et al.*, 1981). Delayed-onset dystonia is recognized after perinatal cerebral anoxia (Burke *et al.*, 1980), and was seen in Cases 25 and 26 in the present series, both of whom had hemiatrophy on CT scan, as did Case 1 of Burke *et al.* (1980). Perhaps delayed onset dystonia is the result of slowly evolving aberrant neuronal sprouting, stimulated by the original lesion, as suggested by Burke *et al.* (1980).

We felt it justifiable to include patients with posthemiplegic dystonia in the series because their dystonia was identical to that seen in other cases of symptomatic hemidystonia, and because they had lesions similar to those seen in patients with hemidystonia without a prior hemiplegia (with the exception of involvement of the internal capsule).

The purpose of this paper is to analyse those anatomical sites most frequently involved in patients with symptomatic focal or hemidystonia. Localization was most often obtained by CT scan, which may have underestimated the extent of cerebral damage, particularly in vascular lesions. However, the CT scan has provided a means of identifying lesions during life in those with focal or hemidystonia, and is likely to have revealed the regions of greatest cerebral damage. Table 4 analyses the sites of lesions identified in the 28 patients described here. Those patients with single isolated lesions are shown separate from those in whom the lesions involved more than one structure. It is difficult to distinguish lesions of the

TABLE 4. SUMMARY OF DISTRIBUTION OF LESIONS RESPONSIBLE FOR DYSTONIA IN THE PRESENT STUDY

Site of dystonia	*Thalamus*		*Caudate nucleus*		*Lentiform nucleus*		*Internal capsule*		*Cortex*		*Hemiatrophy*	
	Single	*Combined*	*Single*	*Combined*	*Single*	*Combined*	*Single*	*Combined*	*Single*	*Combined*	*Single*	*Combined*
Hemidystonia	1	1	1	6	3	6	—	5	—	2	4	1
Arm dystonia	—	2	—	2	—	2	—	—	—	—	—	—
Hand dystonia	3	2	—	—	—	1	—	1	—	1	—	—
Foot dystonia	—	—	—	2	—	2	—	2	—	1	—	—
Torticollis	—	—	2	—	—	—	—	—	—	—	—	—
Total	4	5	3	10	3	11	0	8	0	4	4	1
	9		13		14		8		4		5	

putamen from those of the globus pallidus in CT scans, so these are combined as the lentiform nucleus. However, the lenticular lesions were often placed laterally and were most likely to involve the putamen more than the globus pallidus. Certainly this was the situation in Cases 2, 7, 8 and 22. In the other 10 patients with lenticular lesions, the globus pallidus as well as the putamen was likely to be involved. However, none of these lenticular lesions appeared to involve the globus pallidus alone.

It is also notable that symptomatic hemidystonia or generalized dystonia has not been identified with isolated cortical or brainstem lesions. Torticollis can be produced by experimental brainstem lesions in animals (Foltz *et al.*, 1959) and is very rarely encountered in patients with syringomyelia or spinal cord tumour (Kiwak *et al.*, 1983). There also is a single report of torticollis which disappeared after surgical resection of a frontal cortical scar (David *et al.*, 1952) and another with torticollis associated with a colloid cyst of the third ventricle (Avman and Arasil, 1969). Blepharospasm also can be produced by lesions of the upper brainstem (Jankovic and Patel, 1983). However, patients with torticollis or blepharospasm due to identified brainstem lesions have not been reported to develop more widespread dystonia.

To extend the number of cases, Tables 5 and 6 summarize other patients with focal or hemidystonia described in the literature, either with CT scan localization (13 patients) (Table 5) or pathological verification (7 patients) (Table 6). The cases

TABLE 5. SYMPTOMATIC DYSTONIA WITH CT SCAN LESIONS IN THE LITERATURE

Author		*Site of dystonia*	*Aetiology and pathology*	*Topography*
1 Messimy *et al.* (1977)		L arm dystonia	Traumatic haemorrhage	Head of R caudate nucleus
2 Maki *et al.* (1980)		Transitory L torticollis (4 days)	Trauma	Infarction of R caudate and putamen
3 Mauro *et al.* (1980)	1	R hemidystonia	Traumatic infarction	Atrophy L caudate nucleus (head)
	2	L hemidystonia	Traumatic infarction	R putamen
4 Grimes *et al.* (1982)	1	L arm dystonia	Infarction	R caudate nucleus and putamen
	2	L arm dystonia	Infarction	R caudate nucleus and putamen
	3	L hemidystonia	Infarction	R lenticulocapsulocaudate
5 Demierre and Rondot (1983)	1	R hemidystonia	Trauma Angioma? Infarction	L lenticulocapsulocaudate infarction
	2	L hemidystonia	Infarction	R lenticulocapsulocaudate
	3	L hemidystonia	Embolic infarction	R lenticulocapsulocaudate
6 Russo (1983)		L arm dystonia	Infarction	R lentiform nucleus
7 Traub and Ridley (1982)		L hand dystonia	Infarction	R lentiform nucleus
8 Burton *et al.* (1984)		L hemidystonia	Thromboembolic infarction	R lenticulocapsulocaudate nucleus

TABLE 6. DISCRETE FOCAL LESIONS CAUSING DYSTONIA STUDIED PATHOLOGICALLY IN THE LITERATURE

<table>
<tr><th rowspan="2">Author</th><th rowspan="2">Site of dystonia</th><th rowspan="2">Aetiology</th><th colspan="4">Topography</th></tr>
<tr><th>Thalamus</th><th>Internal capsule</th><th>Striatum</th><th>Globus pallidus</th></tr>
<tr><td>1 Bouttier et al. (1922)</td><td>L forearm and hand. Fixed dystonia</td><td>Fibroma</td><td>R postero-lateral</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>2 Urechia et al. (1942-1943)</td><td>R hemidystonia</td><td>Glioblastoma</td><td>No</td><td>No</td><td colspan="2">L lentiform and caudate nuclei</td></tr>
<tr><td>3 Barraquer-Bordas and van Bogaert (1954)</td><td>L hand. Mobile dystonia</td><td>Tuberculoma</td><td>R ventro-lateral</td><td>Yes</td><td>No</td><td>Internal segment</td></tr>
<tr><td>4 Garcin (1955)</td><td>L hand dystonia</td><td>Infarction</td><td>R postero-lateral</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>5 López Aydillo and Sanz Ibáñez (1956)</td><td>L forearm and hand. Mobile dystonia</td><td>Infarction</td><td>No</td><td>No</td><td>R putamen and head caudate nucleus</td><td>No</td></tr>
<tr><td>6 Denny-Brown (1962)</td><td>R hemidystonia. Mobile</td><td>Infarction</td><td>Left</td><td>No</td><td>L ⅔ putamen, ⅓ caudate nucleus</td><td>No</td></tr>
<tr><td>7 Oppenheimer (1967)</td><td>L fixed hemidystonia</td><td>Infarction</td><td>No</td><td>No</td><td>R putamen and body of caudate nucleus</td><td>No</td></tr>
</table>

shown in Table 6 all had discrete focal lesions. The 5 patients described in the important paper of Dooling and Adams (1975), which will be considered in detail below, are not included for all had widespread cortical infarcts and other pathological changes. It should be noted that when the lentiform nucleus was affected, as judged either by CT scan (Table 5) or pathological examination (Table 6), the putamen was specifically mentioned in 7 of 14 cases. No example of a lesion of the globus pallidus sparing the putamen was recorded in the literature. The data from the present paper and from the literature for a total of 48 patients are combined for analysis in Table 7.

Patients with cerebral hemiatrophy are not informative, for it is impossible to attribute their dystonia to specific anatomical structures. Attention is focused on the remaining patients with discrete lesions. No cases of symptomatic dystonia due to an isolated lesion of the brainstem, internal capsule or cerebral cortex have been found, although the latter structures often are involved in large lesions (the internal capsule on 13 occasions and the cerebral cortex on 4 occasions in the combined material). Small isolated lesions of the thalamus (6 patients), caudate nucleus

TABLE 7. SUMMARY OF DISTRIBUTION OF LESIONS RESPONSIBLE FOR DYSTONIA IN 13 PATIENTS WITH CT SCAN LOCALIZATION AND 7 PATIENTS WITH PATHOLOGY, COMBINED WITH 28 PATIENTS FROM THE PRESENT STUDY

<table>
<tr><th rowspan="2">Site of dystonia</th><th colspan="2">Thalamus</th><th colspan="2">Caudate nucleus</th><th colspan="2">Lentiform nucleus</th><th colspan="2">Internal capsule</th><th colspan="2">Cortex</th></tr>
<tr><th>Single</th><th>Combined</th><th>Single</th><th>Combined</th><th>Single</th><th>Combined</th><th>Single</th><th>Combined</th><th>Single</th><th>Combined</th></tr>
<tr><td>Hemidystonia</td><td>—</td><td>1</td><td>1</td><td>7</td><td>1</td><td>8</td><td>—</td><td>5</td><td>—</td><td>—</td></tr>
<tr><td>Arm dystonia</td><td>1</td><td>—</td><td>1</td><td>3</td><td>1</td><td>3</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>Hand dystonia</td><td>1</td><td>1</td><td>—</td><td>—</td><td>1</td><td>1</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>Foot dystonia</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>Torticollis</td><td>—</td><td>—</td><td>—</td><td>1</td><td>—</td><td>1</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>Total</td><td>2</td><td>2</td><td>2</td><td>11</td><td>3</td><td>13</td><td>0</td><td>5</td><td>0</td><td>0</td></tr>
<tr><td></td><td colspan="2">4</td><td colspan="2">13</td><td colspan="2">16</td><td colspan="2">5</td><td colspan="2">0</td></tr>
<tr><td>Data in Table 7 combined with Table 4</td><td>6</td><td>7</td><td>5</td><td>21</td><td>6</td><td>24</td><td>0</td><td>13</td><td>0</td><td>4</td></tr>
<tr><td></td><td colspan="2">13</td><td colspan="2">26</td><td colspan="2">30</td><td colspan="2">13</td><td colspan="2">4</td></tr>
</table>

(5 patients) or lentiform nucleus (6 patients) were found to produce dystonia. Larger lesions causing dystonia involved the thalamus on 7 occasions, the caudate nucleus on 21 occasions, and the lentiform nucleus on 24 occasions. Combining small and large lesions causing dystonia reveals that the thalamus was involved on 13 occasions, the caudate nucleus on 26 occasions and the lentiform nucleus on 30 occasions. The frequency of involvement of these structures in the present study was very similar to that reported in the literature. We conclude that symptomatic dystonia may be produced by lesions in the thalamus, or the caudate or lentiform nuclei (particularly the putamen), or in a combination of these structures.

This conclusion confirms the earlier proposition of Dooling and Adams (1975), based upon pathological study of 4 patients with severe posthemiplegic dystonia. 'The principle lesion lay in the striatum in each of the 4 cases. The dorsolateral part of the caudate nucleus and the dorsolateral or lateral parts of the putamen had been destroyed. . . . The lesion was much more extensive in the putamen than in the caudate. The globus pallidus was largely intact.' In addition, there was loss of striopallidal and pallidothalamic fibres, and retrograde cell degeneration in the thalamus (nuclei ventralis lateralis, ventralis anterior and centrum medianum). Grimes *et al.* (1982) also commented on thalamic atrophy in CT scans of their 3 patients with posthemiplegic dystonia. Dooling and Adams (1975) compared their findings with those in 9 cases of adult-onset hemiplegia without dystonia, noting the additional extensive involvement of the internal capsule and subcortical white matter in the latter cases. They concluded that 'the essential anatomical lesion in our cases of hemiathetosis was an extensive involvement of the striatum, secondary involvement of striatopallidal fibres and to some extent of the ventral and lateral thalamic nuclei, and a relative preservation of the descending cortical motor pathways'. To this we would add from our data that isolated thalamic lesions also may cause hemidystonia, particularly involving the hand, as had been remarked by Bouttier *et al.*, (1922), Garcin (1955) and perhaps by Barraquer-Bordas and van Bogaert (1954).

There is some suggestion that lesions in each of these three structures may cause a different distribution of dystonia. Each of the 3 patients with torticollis (Maki *et al.*, 1980; Cases 3 and 4, present series) had lesions in the caudate nucleus, usually in its head. In the 16 patients with symptomatic dystonia of the hand and arm, the thalamus was involved in 9, alone in 5 (Bouttier *et al.*, 1922; Garcin, 1955; Cases 10, 11 and 12, present series) and combined with the caudate and/or lenticular lesions in the others. However, symptomatic arm dystonia also was caused by an isolated lesion in the caudate nucleus (Messimy *et al.*, 1977), by an isolated lesion in the lentiform nucleus (Traub and Ridley, 1982; Russo, 1983), or by lesions in both the caudate and lentiform nuclei (López Aydillo and Sanz Ibánez, 1956). Symptomatic focal foot dystonia was uncommon; the caudate nucleus was involved in 1 patient (Case 14), the lentiform nucleus in another (Case 9) and both in a third (Case 20).

Most patients exhibited symptomatic hemidystonia involving both the arm and leg (26 of the 48 patients). Such hemidystonia was caused by isolated lesions of the thalamus (Case 13), the caudate nucleus (Case 1 of Mauro *et al.*, 1980; Case 6), the putamen or lentiform nucleus (Case 2 of Mauro *et al.*, 1980; Burton *et al.*, 1984; Cases 2, 5, 7, 8) or by larger lesions involving these three structures, or by generalized hemiatrophy. It is difficult on the basis of these observations to draw any firm conclusions on topographical localization of dystonia with lesions in different sites. The type of dystonia produced by lesions of thalamus, caudate nucleus or lentiform nucleus was very similar. Lesions at any of these three sites could produce spontaneous dystonia, dystonia on action, fixed dystonic postures, or a combination of all types of dystonia.

Mention must be made of symptoms and signs that were not present in these patients. Despite extensive unilateral striatal and thalamic lesions, none of the patients exhibited dysphasia (9 of our 28 cases and 4 of the 20 cases in the literature had lesions in the left hemisphere). None had evidence of obvious incapacitating cognitive change or of postural instability. None had hemichorea or hemiballism, although both are recognized complications of unilateral basal ganglia lesions.

How could lesions of thalamus, caudate nucleus or lentiform nucleus produce dystonia? These three structures are intimately related. The caudate nucleus and putamen project topographically to the globus pallidus, which itself projects to the thalamus. The resolution of CT scanning, or of pathological findings, makes it difficult to identify specific areas of these structures damaged in symptomatic hemidystonia, but it is reasonable to assume that the region of the thalamus involved is that to which the globus pallidus projects. Lesions in all three sites that may cause symptomatic focal or hemidystonia have in common their ability to disrupt the thalamic input to frontal cortex, and ultimately to the motor area. Accordingly, it seems likely that dystonia is due to delivery of inappropriate commands to premotor and motor cortex. The major output to frontal cortex from those regions of the thalamus that receive basal ganglia input is to the premotor cortex, including the supplementary motor area. Dystonia therefore may be viewed as a consequence of release of premotor cortical activity from thalamic control. We believe that the data presented here suggest that idiopathic dystonia may be due to some unidentified lesion (perhaps biochemical) in the thalamus, caudate nucleus or lentiform nucleus (particularly the putamen).

ACKNOWLEDGEMENTS

We are grateful to the many physicians who have referred patients with dystonia to us for evaluation.

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(*Received August 31, 1984. Revised October 25, 1984. Accepted October 30, 1984*)

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NONHAEMORRHAGIC THALAMIC INFARCTION

CLINICAL, NEUROPSYCHOLOGICAL AND ELECTROPHYSIOLOGICAL FINDINGS IN FOUR ANATOMICAL GROUPS DEFINED BY COMPUTERIZED TOMOGRAPHY

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SUMMARY

Twenty-five patients with nonhaemorrhagic infarcts of the thalamus were studied clinically and by neuropsychological testing, computerized tomography and somatosensory evoked response (SER) recordings. Our aim was to determine whether the findings in these different tests would form distinct symptom clusters associated with different anatomical territories of the thalamus.

Infarction conforming to the tuberothalamic arterial territory caused a facial paresis for emotional movements, severe neuropsychological deficits and a delay of the SER after P14. Infarction conforming to the interpeduncular profundus arterial territory caused a supranuclear vertical gaze paresis, severe neuropsychological deficits and a delay in the P60 component of the SER. Infarction conforming to the anterior choroidal territory caused a hemiparesis, moderate neuropsychological deficits and varied sensory evoked responses. Patients with infarctions conforming to the entire geniculothalamic territory had sensory loss in multiple modalities, minimal neuropsychological deficits and absence of sensory evoked responses after P14. A lacune in this territory caused pure hemisensory loss involving part of the body for the modalities of pain and light touch but not proprioception or vibration. Neuropsychological deficits were uncommon and N32 and N60 were delayed in the SER.

INTRODUCTION

We have recently studied 25 patients with nonhaemorrhagic thalamic infarctions by computerized tomography (CT), and by clinical, neuropsychological and electrophysiological procedures. Our aim was to determine if, when we grouped the patients according to location of lesion as determined by CT, consistent clusters of clinical, neuropsychological and SERs would emerge in relation to the different sites of damage.

METHODS

Computerized Tomography

We prepared templates of 4 mm brain slices through the thalamus and surrounding areas. The templates were based on our own human brain sections and on the Roberts and Hanaway Atlas (1970). Abnormal images detected on the CT scan were plotted on the appropriate templates by one of the investigators blind to clinical, neuropsychological and SER data. A composite of the vascular territories on 4 mm thalamic templates is seen in fig. 1.

Clinical and Neuropsychological Studies

Twenty-five patients were examined neurologically, of which 23 underwent the following battery of neuropsychological tests: Temporal Orientation (Benton *et al.*, 1983); WAIS-R (Wechsler, 1981); Multilingual Aphasia Examination (Benton and Hamsher, 1978); Wechsler Memory Scale (Wechsler, 1945) (prorated without the visual reproduction subtest); Benton Visual Retention Test—Administration A, Form C (Benton, 1974); Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1945) (copy and delayed recall); Rey Auditory Verbal Learning (Rey, 1964); Facial Recognition (Benton and Van Allen, 1968); and Judgment of Line Orientation (Benton *et al.*, 1978). Estimation of IQ, language, short-term memory and visual perception was based on the results of these tests.

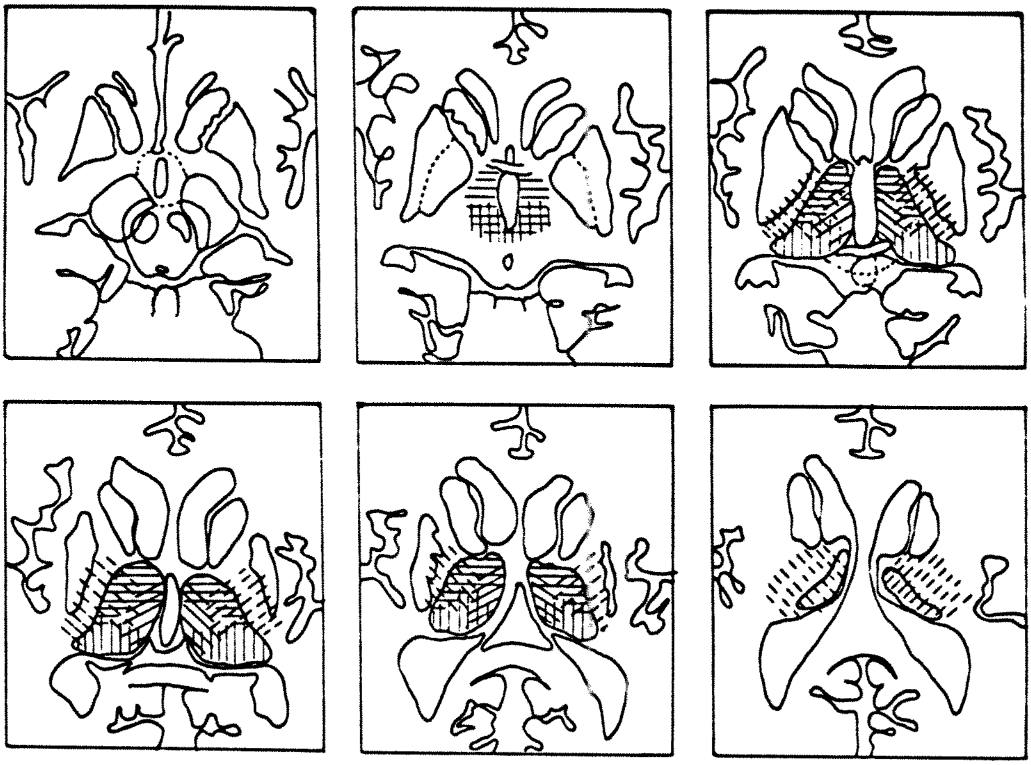


FIG. 1. Templates (4 mm) through the thalamus depicting the following four arterial territories. Vertical hatching = geniculothalamic territory; horizontal hatching = tuberothalamic territory; unbroken diagonal hatching = interpeduncular profundus territory; broken diagonal hatching = anterior choroidal territory.

Somatosensory Evoked Responses

The electrophysiological studies were performed by another investigator, also blind to CT, clinical and neuropsychological findings: silver/silver chloride disc electrodes were attached according to the 10-20 International System at F_3, F_4, C_3, C_4, P_3, P_4, O_1, O_2, F_7, F_8, T_3, T_4, T_5, T_6, and between the sixth and seventh cervical spines with an impedance of less than 5 KΩ. Linked ears served as the reference. The median nerve was stimulated at the wrist with a pulse duration of 0.1 ms at a rate of 2.5/s. The intensity was adjusted to elicit a modest twitch of abductor pollicis brevis. The input was amplified by a 16-channel Grass EEG Recorder, Model 5P11. The frequency response was 3 to 1000 Hz (3 dB down). The output was summated by a 21MX Hewlett Packard computer. The analysis time was 95 ms with a delay of 5 ms and the digitizer sampling time was 0.2 ms. There were four tests, each consisting of 1500 stimulations of the median nerve, left, right, and bilateral twice. The computer was programmed to edit out responses with seven successively overloaded points, so that potentials with unrealistically large potentials contaminated by ECG or muscle artefacts were deleted. The results were plotted on an x-y plotter.

Yamada *et al.* (1984*b*) have recently reported that the latency of the first and second negative waves is different in frontal, central and parietal regions. In the frontal region these latencies are 17 and 29 ms, respectively, in the central region, 19 and 32 ms, and in the parietal region, 20 and 34 ms. They found that unilateral stimulation is reliable for assessment of early components (N17, N19, N20) but not later components (N32, N34, N60) because of intertrial variability of the latter in normals. However, bilateral stimulation normally causes symmetrical late responses and thus can be used to assess the later components. Bilateral stimulation was not helpful in assessing P14 and frontally recorded N17 and N29, since they are distributed bilaterally, even with unilateral stimulation. It would be expected that with bilateral median nerve stimulation, SERs recorded over each hemisphere should be the amalgam of both sets of stimulation. In practice, however, Yamada and coworkers (1983, 1984*a*, *b*) have not found this to be entirely true. With bilateral stimulation, the SER recorded over each hemisphere is predominantly from the contralateral hand, as if with bilateral stimulation there is an impediment to the ipsilateral components. However, we only used bilateral stimulation in conjunction with unilateral stimulation. The former is especially helpful in confirming abnormalities of the later SERs (N32, N34 and N60) which, as mentioned earlier, have significant intertrial variability with unilateral stimulation but not with bilateral stimulation. Measurements in milliseconds were made to P14 and the subsequent negative waves at each of the following areas: N17, N29 at frontal, N19, N32 and N60 at central and N20, N34 and N60 at parietal electrodes. We compared latencies of the left and right sides as well as latencies established for normals in our laboratory (normal +3 SD). The details of normal features and abnormal criteria of topographic SEP recordings are described elsewhere (Yamada *et al.*, 1984*b*).

RESULTS

Anatomical Findings

On the basis of CT data the patients were divided into four groups. The anatomical findings for each group are given in the following order: number of cases, site of lesion and probable arterial territory. For each group a CT scan and a diagram depicting the usual territory of the artery probably involved in the infarcts are shown.

Posterolateral thalamic infarcts ($n = 9$). The lesions were situated posterolaterally in the thalamus in the territory of the geniculothalamic artery. Fig. 2A shows a CT scan and fig. 2B the arterial territory for this group. In 4 of the 9 patients there was

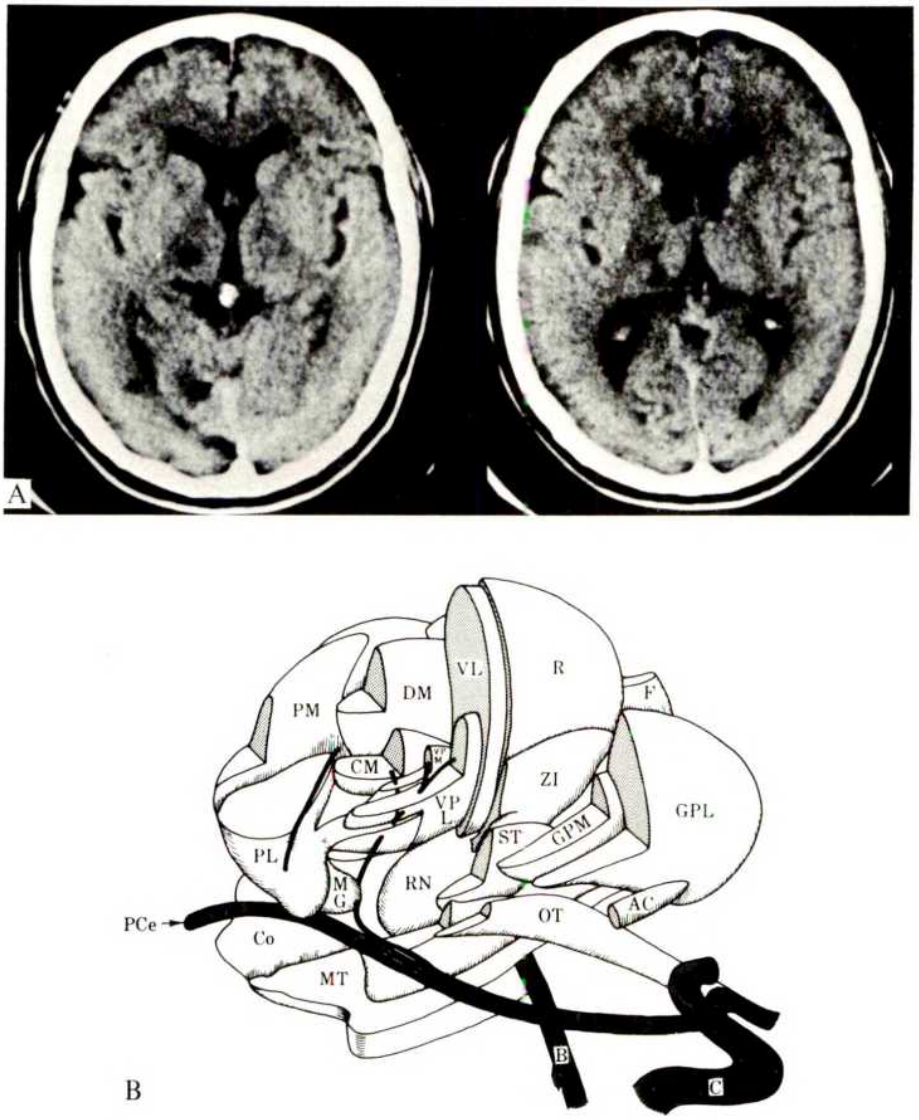


FIG. 2A. CT scan from *Case 8* showing infarction in the geniculothalamic arterial territory. Note the concomitant posterior cerebral artery infarction. B, territory of the geniculothalamic artery. This is based upon the Schlesinger Atlas (1976), fig. 27.4 and 27.5. A = anterior nucleus; AC = anterior commissure; AV = anteroventral nucleus; B = basilar artery; C = carotid artery; CM = centrum medianum; Co = colliculi; DM = dorsomedial nucleus; DP = deep interpeduncular profundus artery; F = fornix; GPL = globus pallidus (lateral); GPM = globus pallidus (medial); LG = lateral geniculate; LP = lateroposterior nucleus; MG = medial geniculate; MAM = mammillary bodies; MT = midbrain tegmentum; MTT = mammillothalamic tract; OT = optic tract; PCe = posterior cerebral artery; PCo = posterior communicating artery; PL = pulvinar (lateral); PM = pulvinar (medial); Pu = pulvinar; R = reticular nucleus; RN = red nucleus; ST = subthalamic nucleus; Tt = tuberothalamic artery; VL = ventrolateral nucleus; VPL = ventral posterolateral nucleus; VPM = ventral posteromedial nucleus; ZI = zona inserta. (Abbreviations for figs. 2B, 4B, 5B and 6B.)

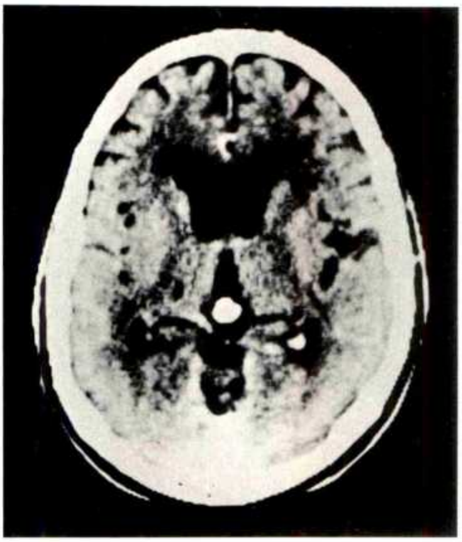


FIG. 3. CT scan of *Case 8* showing a lacune in the geniculothalamic territory seen only in one cut.

also infarction in the posterior cerebral artery territory. Lacunes may also occur in this territory. CT scanning is often negative, but with 4 mm cuts on a high resolution scanner we were able to demonstrate lacunes in 4 cases (fig. 3).

Anterolateral thalamic infarction (n = 5). These are located in the territory of the tuberothalamic artery (also termed the polar artery by Percheron, the anterior internal optic artery by Duret and the premamillary pedicle by Foix and Hillemand, as quoted by Castaigne *et al.*, 1981). Two of our patients developed their infarct postoperatively after clipping of giant posterior communicating artery aneurysms. An example of a CT scan for this group is shown in fig. 4A and the arterial territory in fig. 4B.

Medial thalamic infarction (n = 3). These are in the territory of the deep interpeduncular profunda arteries (also termed the paramedian thalamic arteries by Percheron, the posterior internal optic arteries by Duret and the thalamoperforating pedicle by Foix and Hillemand, as quoted by Castaigne *et al.*, 1981). An illustrative CT scan is shown in fig. 5A and the usual arterial territory in fig. 5B. Note that one interpeduncular profundus artery may supply the medial thalamus bilaterally and thus lead to bilateral thalamic infarction. We have seen two such examples.

Lateral thalamus and posterior internal capsule (n = 8). These patients had lesions in the posterior capsule which extended into the thalamus (fig. 6A). The lesion may involve part or the whole anterior choroidal territory (fig. 6B).

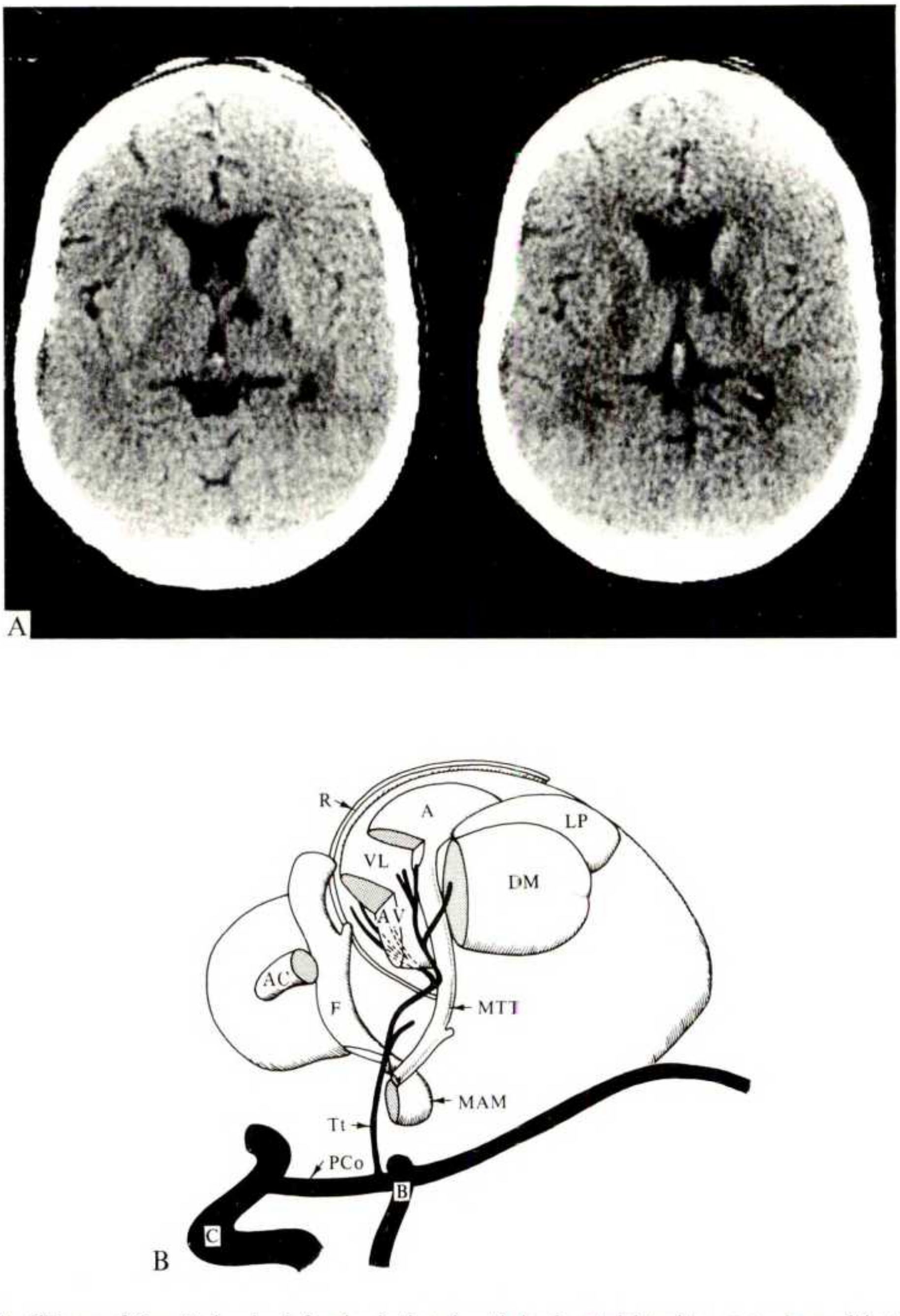


FIG. 4A. CT scan of *Case 14* showing infarction in the tuberothalamic arterial territory. B, territory of the tuberothalamic artery. This is based on fig. 28.4 of the Schlesinger Atlas (1976). Abbreviations are as for fig. 2B.

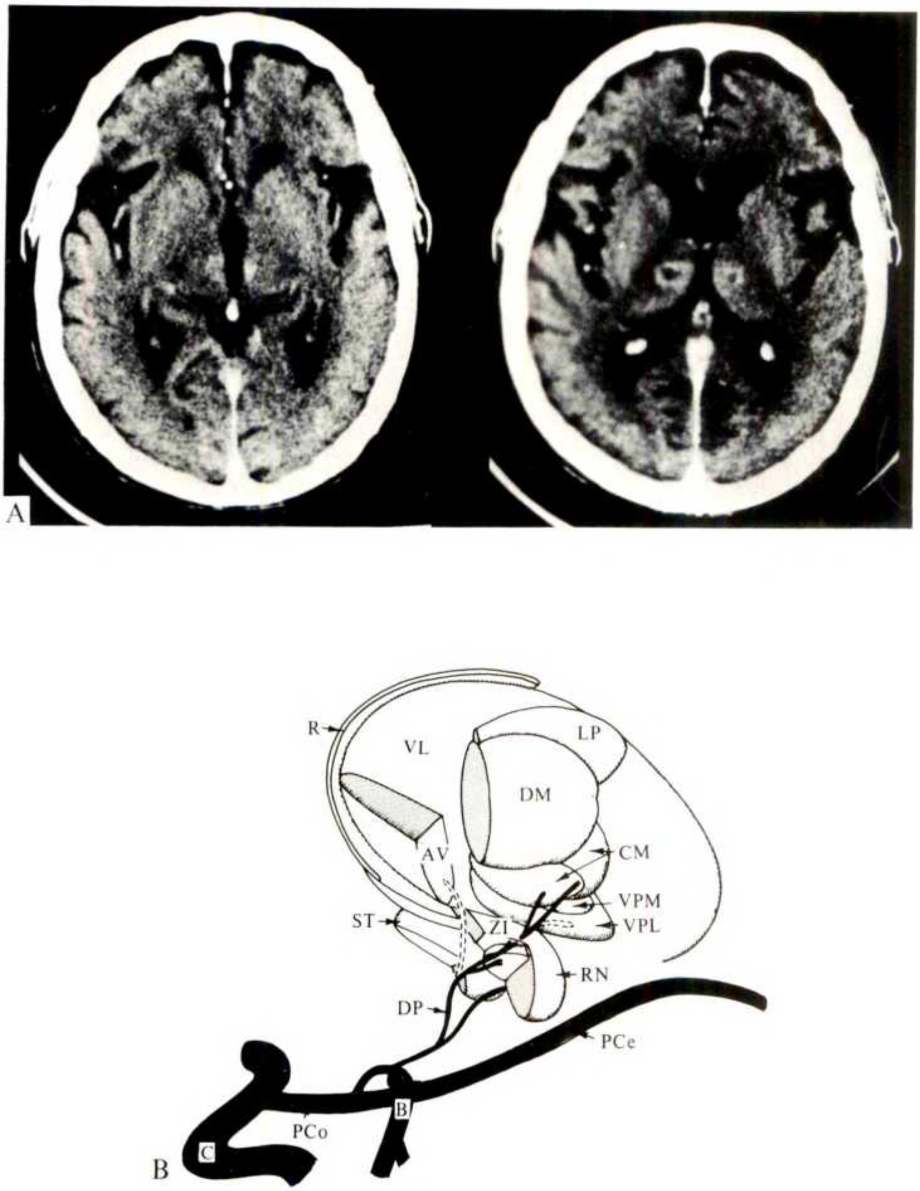


FIG. 5A. CT scan of *Case 17* showing infarction in the interpeduncular profundus arterial territory. Note the bilateral lesions. This scan is contrast enhanced. B, territory of the interpeduncular profundus artery. The dotted lines indicate other areas which may also be supplied by this artery. This is based on fig. 28.6 and 28.7 of the Schlesinger Atlas (1976). Abbreviations are as for fig. 2B.

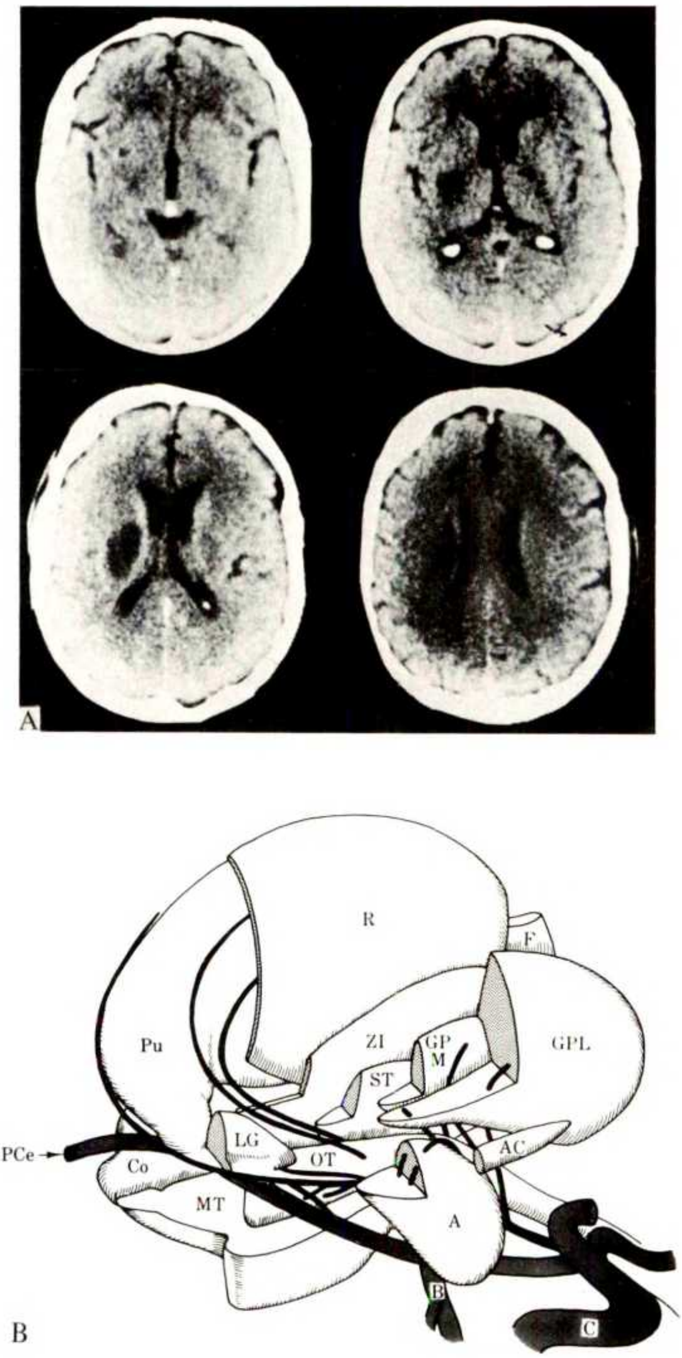


FIG. 6A. CT scan of *Case 23* showing infarction in the anterior choroidal arterial territory. B, the territory of the anterior choroidal artery. This is based on fig. 27.2 of the Schlesinger Atlas (1976). Abbreviations are as for fig. 2B.

Clinical and Neuropsychological Findings

The clinical and neuropsychological features of these cases are summarized in Tables 1 and 2; further clinical data and the actual neuropsychological test scores are given in the Appendix. Additional findings, divided by group, are as follows.

Posterolateral thalamic infarction. Cases 1, 2, 7 and 9 had concomitant posterior cerebral artery infarction. The patients have been divided into two subgroups, first those with probable complete geniculothalamic infarction (the first 4 patients in Tables) and, secondly, those with partial geniculothalamic territory infarction (Cases 5 to 9 in Tables).

Sensory loss for several modalities was present in all 4 patients in the first subgroup and is the clinical hallmark of this category. However, 1 also had dysaesthesia, 2 had hemipareses and 2 had visual field defects. In addition to thalamic damage, Cases 1 and 2 had sustained associated infarctions in the territory of the posterior cerebral artery. Our behavioural assessment of Case 1 revealed a severe left-sided hemispatial neglect and poor attention span leading to overall poor neuropsychological performances. Case 2 was not formally examined with neuropsychological tests. The remaining 2 patients (Cases 3 and 4) had no concomitant posterior cerebral infarction on CT scan, no visual field defects and only mild neuropsychological impairment. Case 4 illustrates this subgroup.

A 58-year-old right-handed woman suffering from myotonic dystrophy noted the sudden onset of left-sided numbness on June 16, 1982. She was admitted to hospital and on examination found to have cataracts, percussion myotonia and proximal weakness. These were long-standing deficits. Her mental status was normal, as were her cranial nerves. Her tendon reflexes were diminished but symmetrical; plantar reflexes were flexor. She had loss of sensation on her left side for pinprick, light touch, proprioception, vibration, two-point discrimination, graphaesthesia and stereognosis. No hyperaesthesia or dysaesthesia was noted. Her left hand showed pseudoathetoid movements with her eyes closed. Neuropsychological testing demonstrated difficulties with short-term visual memory for designs, constructional copy and recall of the Rey-Osterrieth complex figure, and controlled oral word association. The remainder of the examination was normal, including visual perceptual, intellectual, linguistic and short-term verbal memory abilities. There was no clinically significant amnesia or aphasia.

The 5 patients with partial lesions in the geniculothalamic territory had either decreased pinprick or light touch appreciation, without loss for proprioception or vibration, involving only part of the contralateral body, for example for the face only in Case 9, the leg only in Case 6 and the face and arm only in Case 8. None had hemiparesis but 3 had visual field defects. Clinical assessment of mental status and neuropsychological testing revealed no remarkable deficits except for the patients with posterior cerebral artery infarction who had visual memory and visual perceptual deficits. Case 8 is an illustrative example of this subgroup.

A 65-year-old right-handed clinical psychologist suddenly developed right-sided paraesthesiae. On examination he had right hemisensory loss for pinprick involving the face and hand but not the leg. Testing for vibration sense, proprioception, graphaesthesia and stereognosis in the right hand was normal. No motor deficits were noted. On clinical testing his mental status was normal.

TABLE 1. CLINICAL FINDINGS

Case No	Age/Sex	Handedness	Side of infarction	Muscle strength	Plantar reflexes	Pinprick	Light touch	Proprioception	Vibration	Dysaesthesia	Visual field defect
Posterolateral thalamic infarction											
1	48/F	R	R	Decreased	Extensor	Decreased	Decreased	Decreased	Decreased	No	Yes+
2	78/F	R	R	Decreased	Extensor	Decreased	Decreased	Decreased	Decreased	Yes	Yes+
3	64/F	L	R	Normal	Flexor	Decreased	Decreased	Decreased	Decreased	No	No
4	58/F	R	R	Normal	Flexor	Decreased	Decreased	Decreased	Decreased	No	Yes
5	66/M	R	R	Normal	Flexor	Decreased*	Decreased*	Decreased*	Normal	Yes	No
6	19/M	R	R	Normal	Flexor	Decreased	Decreased	Normal	Normal	Yes	Yes
7	68/M	R	R	Normal	Flexor	Normal	Normal	Normal	Normal	No	Yes+
8	65/M	R	L	Normal	Flexor	Decreased	Decreased	Normal	Normal	No	No
9	60/M	R	L	Normal	Flexor	Decreased**	Decreased**	Normal	Normal	Yes	Yes+
Anterolateral thalamic infarction											
10	67/M	R	L	Decreased	Extensor	Normal	Normal	Decreased	Normal	No	Yes
11	75/M	R	L	Normal	Flexor	Normal	Normal	Normal	Normal	No	No
12	66/F	R	L	Normal	Flexor	Normal	Normal	Normal	Normal	No	Yes
13	67/F	R	R	Decreased	Extensor	Normal	Normal	Normal	Normal	No	No
14	60/F	R	R	Decreased	Extensor	Normal	Normal	Normal	Normal	No	No
Medial thalamic infarction											
15	69/F	R	Bilateral	Normal	Extensor	Normal	Normal	Normal	Normal	No	No
16	74/F	R	R	Decreased	Flexor	Normal	Normal	Normal	Normal	No	No
17	81/M	R	Bilateral	Normal	Extensor	Normal	Normal	Normal	Normal	No	No
Lateral thalamic/posterior limb of internal capsule infarction											
18	58/M	R	R	Decreased	Extensor	Normal	Normal	Normal	Normal	No	No
19	63/F	R	R	Decreased	Extensor	Normal	Normal	Normal	Normal	No	No
20	72/M	R	L	Decreased	Extensor	Normal	Normal	Normal	Normal	No	Yes
21	47/M	R	L	Decreased	Extensor	Decreased	Normal	Normal	Normal	No	No
22	67/M	R	L	Decreased	Extensor	Decreased	Normal	Normal	Normal	No	No
23	58/M	R	L	Decreased	Extensor	Normal	Decreased	Normal	Normal	No	No
24	62/F	R	L	Decreased	Extensor	Decreased	Normal	Normal	Normal	No	No
25	67/M	R	L	Decreased	Extensor	Decreased	Normal	Normal	Normal	No	No

+ Associated posterior cerebral infarct, * foot only; ** lower face only.

TABLE 2 RESULTS OF NEUROPSYCHOLOGICAL TESTING

Case No.	*Age/Sex*	*Years of education*	*Side of lesion*	*Verbal IQ*	*Performance IQ*	*Language*	*Verbal memory*	*Visual memory*	*Visual Perception*	*Other*
Posterolateral thalamic infarction										
1	48/F	10	R	78*	57*	Normal	Normal	—	Impaired	Left neglect, associated posterior cerebral infarct
2	78/F	—	R	—	—	—	—	—	—	Associated posterior cerebral infarct
3	64/F	12	R	116	109	Normal	Normal	Normal	Normal	
4	58/F	12	R	106	99	Normal	Normal	Impaired	Normal	
5	66/M	16	R	117	95*	Normal	Normal	Normal	Normal	
6	19/M	13	R	103	98	Normal	Normal	Normal	Normal	
7	69/M	16	R	120	87*	Normal	Normal	Impaired	Impaired	Associated posterior cerebral infarct
8	65/M	16	L	—	—	—	—	—	—	
9	60/M	11	L	89	88	Normal	Impaired	Impaired	Impaired	Associated posterior cerebral infarct
Anterolateral thalamic infarction										
10	67/M	12	L	67*	71*	Impaired	Impaired	Impaired	Impaired	Disorientation
11	75/M	16	L	69*	75*	Impaired	Impaired	Impaired	Impaired	Disorientation
12	66/F	7	L	—	—	Impaired	Impaired	—	Impaired	Disorientation
13	67/F	8	R	100	76*	Normal	Normal	Impaired	Impaired	Disorientation, dysarthria
14	60/F	8	R	106	76*	Normal	Normal	Impaired	Impaired	
Medial thalamic infarction										
15	69/F	16	R+L	99*	75*	Normal	Impaired	Impaired	Impaired	Disorientation
16	74/F	12	R	78*	61*	Normal	Impaired	Impaired	Impaired	Left neglect, disorientation
17	81/M	12	R+L	81*	65*	Normal	Impaired	Impaired	Impaired	
Lateral thalamic/posterior limb of internal capsule infarction										
18	58/M	12	R	95*	87*	Normal	Normal	Impaired	Impaired	
19	63/F	12	R	106	80*	Normal	Normal	Impaired	Impaired	
20	72/M	8	L	81	87	Impaired++	Impaired	Impaired	Normal	Dysarthria
21	47/M	12	L	111	112	Normal	Impaired	Impaired	Normal	
22	67/M	8	L	104	114	Impaired++	Impaired	Impaired	Normal	Dysarthria Slow reading of paragraphs
23	58/M	12	L	93*	88*	Impaired++	Impaired	Impaired	Normal	Dysarthria, occasional paraphasia
24	62/F	9	L	84	87	Normal	Impaired	Impaired	Normal	Dysarthria
25	67/M	12	L	92	87	Normal	Impaired	—	Normal	Dysarthria

* Below estimated IQ based on educational level and occupational background, — not available, ++ mild difficulties with some tasks in Multilingual Aphasia Battery but not conforming to aphasic syndrome

Anterolateral thalamic infarction. All 5 patients had normal sensory findings save for transient proprioceptive loss in Case 8; 3 had hemipareses and 2 visual field defects. One with a visual field defect had also had posterior cerebral artery infarction. This group had severe and wide-ranging neuropsychological deficits in language, temporal orientation, intellect, memory, and visual perception and constructional praxis when the left side was affected. With right anterolateral thalamic infarction, nonverbal intellect, visuoperceptual performance, constructional praxis and visual memory for designs were compromized, with preservation of verbal functions, such as verbal intellect, speech, language processing and short-term verbal memory. All patients with left-sided lesions were disorientated; those with right-sided lesions were not. Case 10 illustrates this group.

A 67-year-old right-handed man suddenly developed right-sided weakness, difficulty in speaking and confusion. Examination revealed normal sensation for pinprick, light touch and vibration sense, but mild proprioceptive loss in the right hand. The latter had resolved by six weeks. There was a right facial paresis for emotional movements and a right hemiparesis. Neuropsychological testing six weeks after the event revealed pervasive impairments in speech and language characteristic of thalamic aphasia (Graff-Radford and Damasio, 1984), verbal and nonverbal intelligence, anterograde as well as retrograde memory for verbal and nonverbal material, temporal orientation, visual perception and constructional praxis. The patient continued to improve and was retested two years later. At this time speech and language testing were improved but the patient was still mildly aphasic; intellect, visual perception, praxis, orientation and memory had also improved but were still in the borderline to low average range.

Medial thalamic infarction. The 3 patients in this group had no sensory deficit. One had a hemiparesis, none had visual field defects. In the initial stages, speech and language were intact but intellect, memory, visual perception, constructional praxis and temporal orientation were impaired. One case (No. 16) had a visual neglect syndrome. All 3 had supranuclear vertical gaze paresis. Case 15 is the example from this group.

A 69-year-old right-handed retired school teacher suddenly developed confusion, dysarthria and lethargy. Initially she had a waxing and waning level of attention. Examination showed a supranuclear vertical gaze paresis but normal sensory and motor function. Neuropsychological testing six weeks later revealed a euphoric woman who was disorientated for time and place and strikingly amnesic. Her memory was poor for both anterograde and retrograde material. Speech, naming, repetition and writing were normal and there was no evidence of aphasia. Verbal intellect was well preserved while nonverbal intellect was clearly impaired. Visual perceptive discrimination of unfamiliar faces, visuospatial judgement, constructional praxis and right-left orientation on confrontation were defective. On follow-up examination 18 months later she had improved in many respects but her amnesia remained. Intellectual, perceptual and constructional performances were within or very close to the normal range, but memory had improved little.

Lateral thalamus/posterior limb of internal capsule. In this group, all 8 patients had a hemiparesis, 4 had diminished pinprick, 1 decreased light touch, but none had impaired proprioception or vibration sense. Only one had a visual field defect. Speech and language were usually spared but controlled oral word association and articulation were affected in about half of the cases. Right-sided lesions could disrupt nonverbal intellect, visual perceptual or spatial discrimination and short-term visual memory for designs. In contrast, the left-sided lesions rarely affected IQ levels, visual perception and constructional praxis. Short-term verbal and visual memory was compromised in about half of the cases; however, these deficits were not associated with any clinically significant amnesia. Case 23 illustrates this group.

On July 4, 1982 a 58-year-old right-handed man suddenly developed a right hemiparesis and slurred speech. On examination, the weakness was greater in his face and arm than his leg. Sensory examination for pain, light touch, proprioception and vibration was intact bilaterally. Neuropsychological examination revealed an alert and well-orientated man without aphasia. Speech was fluent but dysarthric. Naming, repetition, spelling and aural comprehension were normal, but controlled oral word association was impaired and reading comprehension of paragraphs was below expectations. Verbal and nonverbal intellect appeared to have declined modestly, as did short-term memory for verbal material and geometric designs. Facial discrimination, judgement of line orientation and constructional praxis were normal. Neuropsychological examination one year after onset showed improved intellectual performance, controlled oral word association, reading and short-term memory. Mild residual deficits in Rey's verbal memory test and in visual memory for designs were observed but he was not clinically amnesic. Some improvement in the strength of the right side was apparent. An arteriogram showed an absent left anterior choroidal artery.

Somatosensory Evoked Responses

Major findings are tabulated in the Appendix.

Posterolateral thalamic infarction. This group will again be subdivided into those patients with infarction involving the complete geniculothalamic territory and those with involvement of only part of the territory.

Complete geniculothalamic territory. Unilateral median nerve stimulation of the affected arm resulted in no response after P14 in both hemispheres. Unilateral median nerve stimulation of the nonaffected arm or bilateral median nerve stimulation caused a normal response in the unaffected hemisphere and an N17 wave over the affected hemisphere (fig. 7A, B, C). In a further patient with a clinically identical picture to this group, CT scan was negative but SERs were of the same pattern as this group.

Partial geniculothalamic territory. We have 5 examples in this group. In 2, N17, N19 and N20 were normal but N29, N32 and N34 and N60 waves were delayed (fig. 8A, B). One patient with the clinical findings of a thalamic lacune (unilateral loss of pinprick sensation) but negative CT scan had an identical SER to this group. One patient had a normal SER. In 2 the SER could not be interpreted because 1 had a severe peripheral neuropathy (Case 7) and the other could not tolerate adequate stimuli (Case 4).

Anterolateral thalamic infarction. In this group there were 4 patients on whom SERs were performed. In 3 there was a delay of N17, N19 and N20 over the frontal, central and parietal areas, respectively. Two of the cases had a delay of N29, N32 and N34; in all, N60 was delayed in the central region but the N60 response varied in each case over the parietal area (fig. 9A, B). In 1 case there was only a delay of N60.

Medial thalamic infarction. In the 3 patients in this group the most consistent delay noted was in the N60 (fig. 10A, B).

Lateral thalamic/posterior limb of internal capsule infarction. Of the 8 patients in this group, 7 had SERs and all had a normal N17 and a delayed N60. However, waves N19, N20, N29, N32, and N34 were variable, making this the most heterogenous group in relation to the SER findings. An example is shown in fig. 11A, B.

DISCUSSION

Although vascular territories are somewhat variable from subject to subject and the extent of infarction within a given territory is also variable, the CT findings in our patients can be grouped according to four fairly distinct loci. Similarly, the findings noted above indicate that the clinical, neuropsychological and electrophysiological profiles associated with these anatomical groups are relatively distinct.

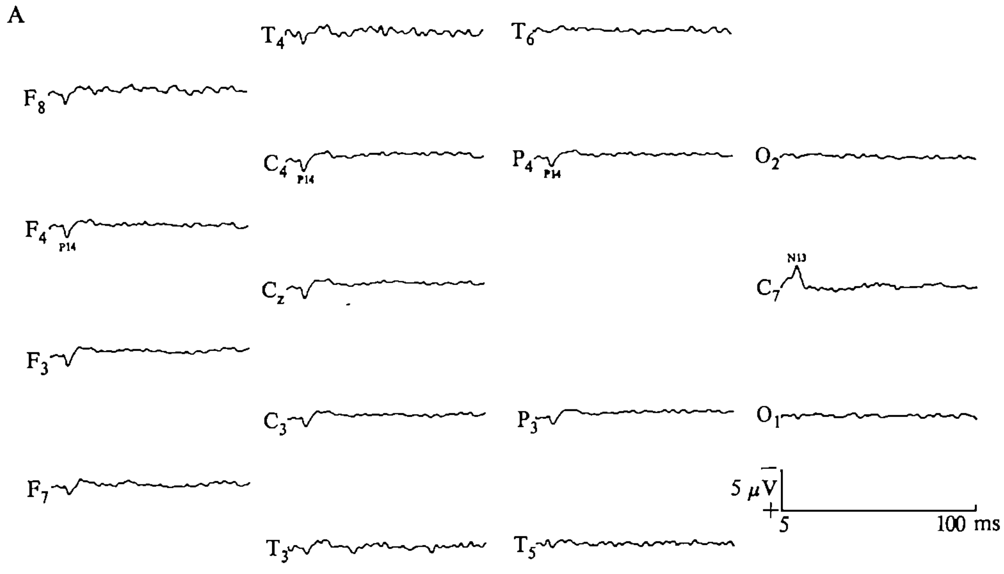
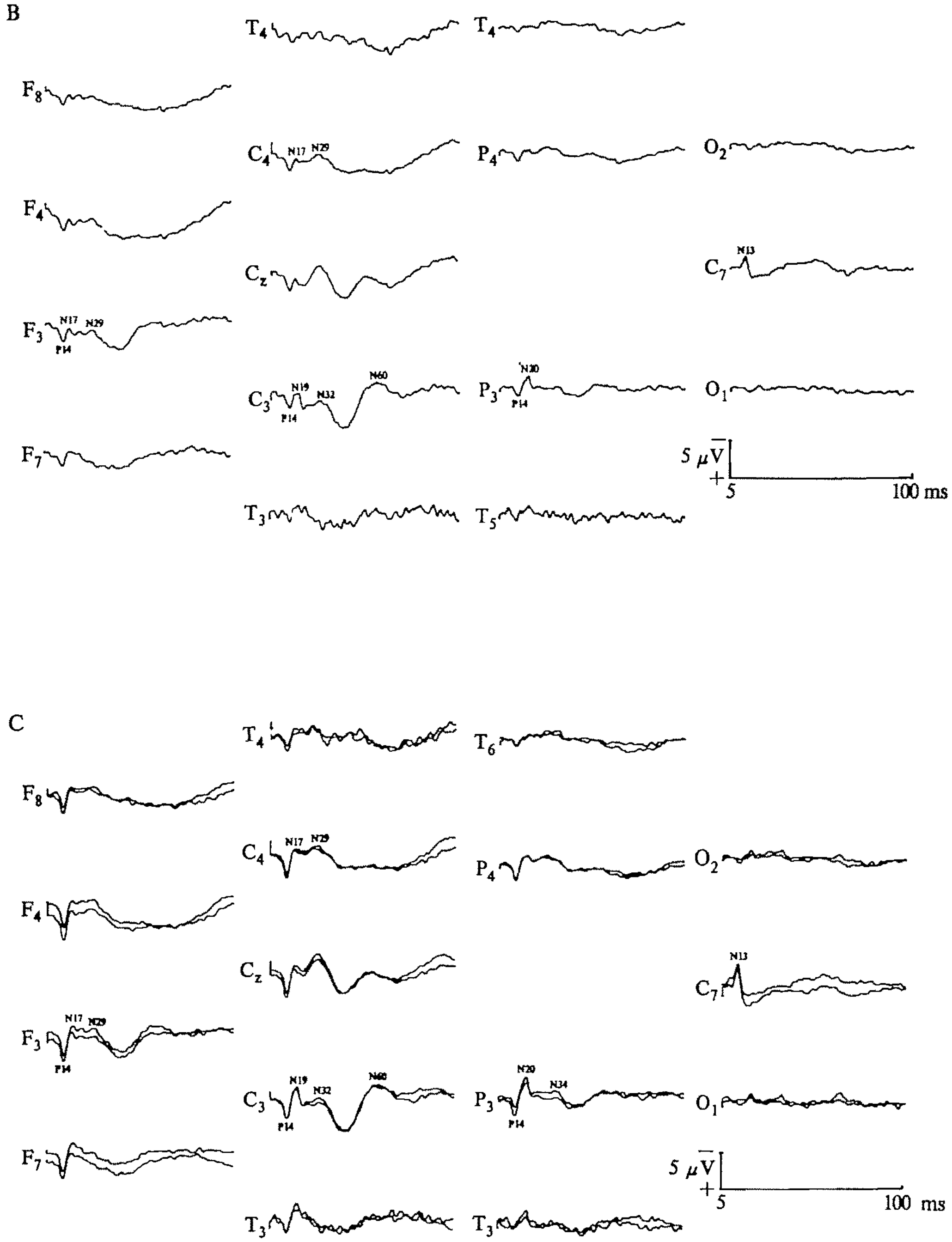


FIG. 7A. Left unilateral stimulation in *Case 1*. Note the complete absence of evoked responses after brainstem P14. B, right unilateral stimulation in *Case 1*. Note the normal contralateral responses over the left hemisphere and some ipsilateral responses over the right hemisphere. C, two trials of bilateral stimulation. They appear identical to those from right unilateral stimulation. Using only bilateral stimulation would have been deceptive in this case because of the ipsihemisphere response from right-sided stimulation.


B
T4
T4
F8
C4 N17 N29
P4
O2
F4
Cz
C7 N13
F3 N17 N29 P14
C3 N19 N32 N60 P14
P3 N20 P14
O1
F7
5 μV
+
5
100 ms
T3
T5
C
T4
T6
F8
C4 N17 N29
P4
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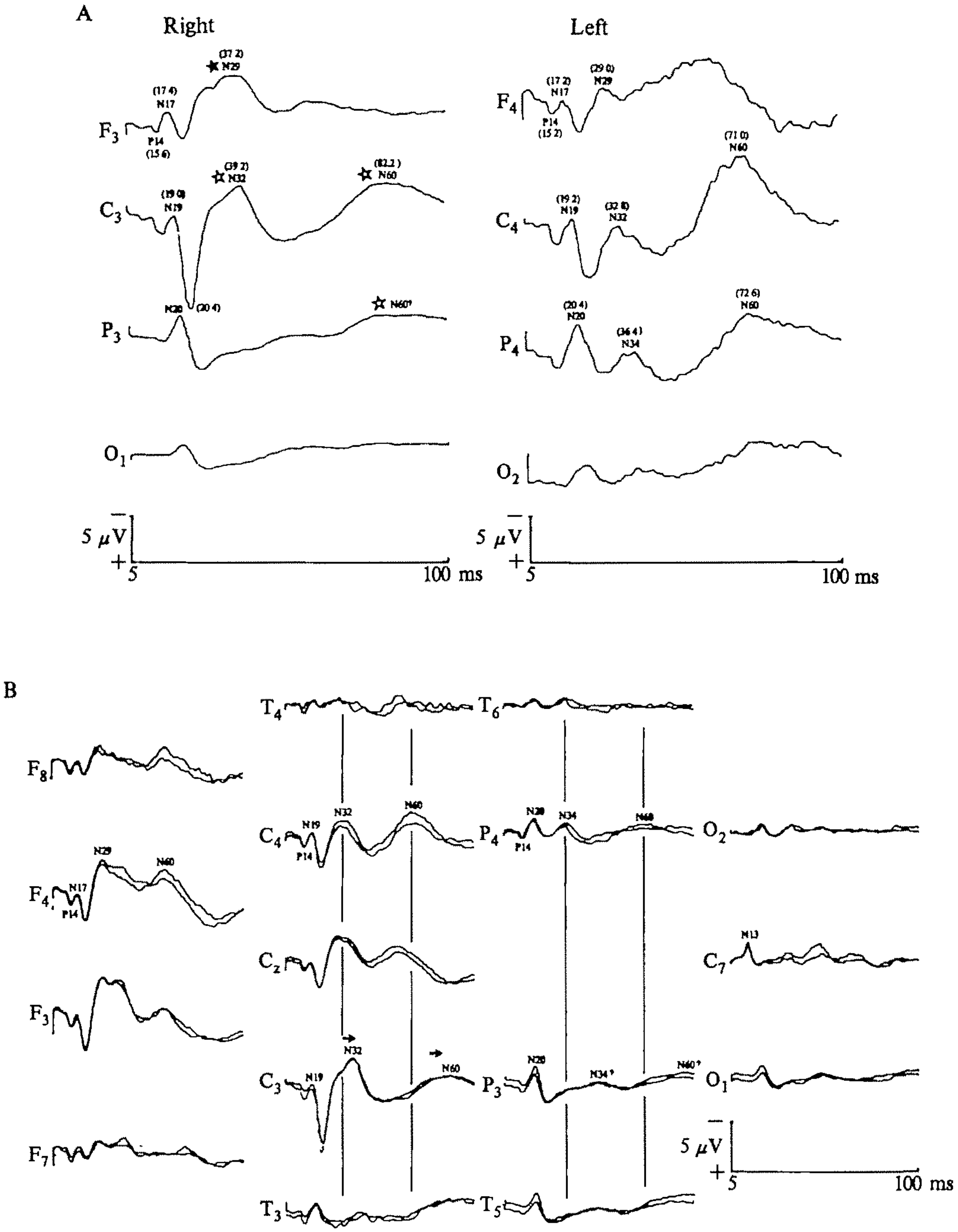

FIG. 8A. Right and left unilateral median nerve stimulation in *Case 8*. The responses to left unilateral stimulation are normal but there is a definite delay in N29 (black star) and a possible delay in N32 and N60 (hollow stars) with right-sided stimulation. B, two trials of bilateral stimulation in *Case 8* which confirm the left hemisphere delay in N32 and N60. Note that the configuration of N32 and N60 at C_3 are almost identical to those with unilateral stimulation.

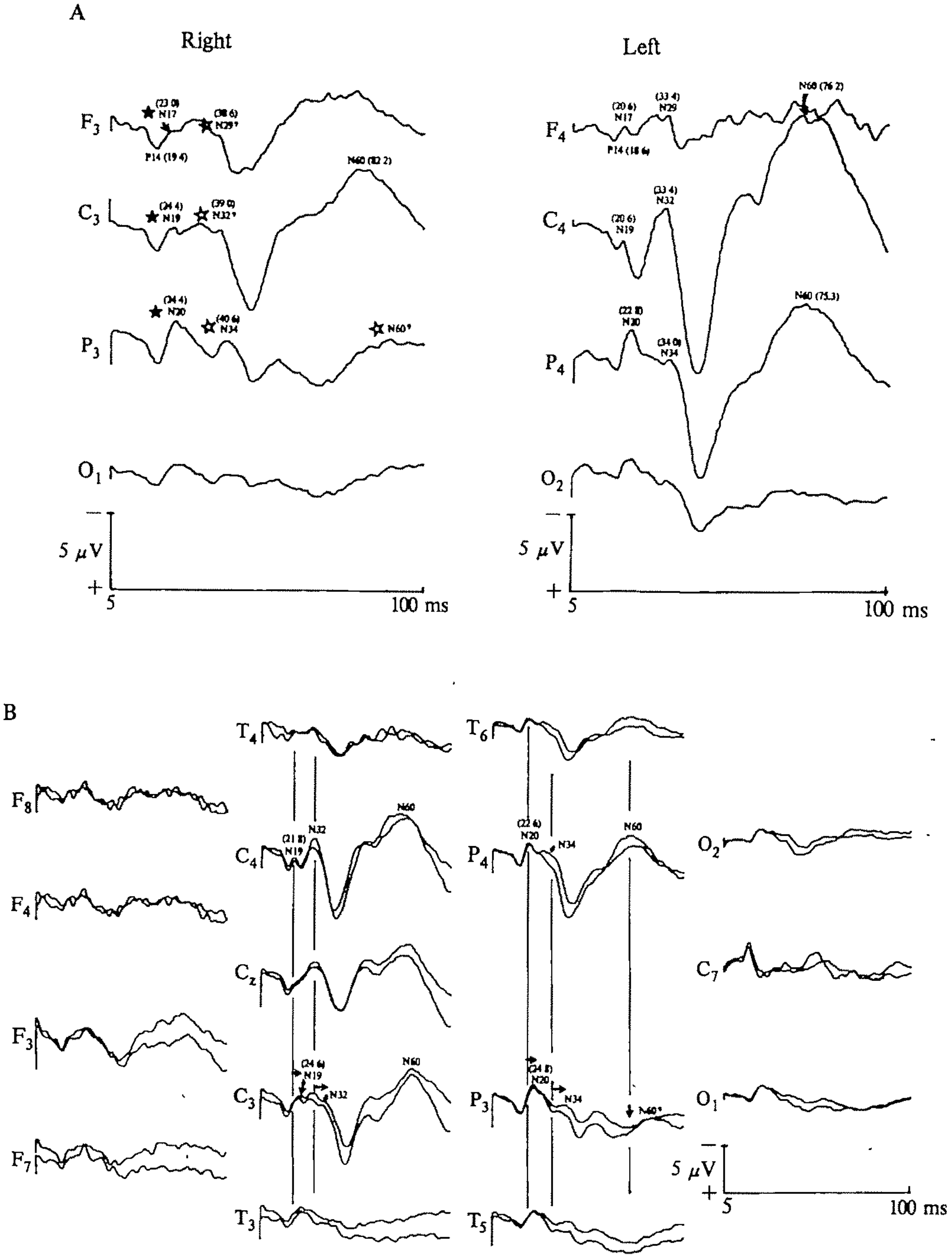

FIG. 9A. Right and left unilateral median nerve stimulation in *Case 10*. Note the normal responses over the right hemisphere and the definite delay in N17, N19 and N20 (solid black stars) and probable delay in N29, N32, N34 and N60 (hollow stars) on the left. B, two trials of bilateral stimulation in *Case 10* which confirm both the earlier and later wave delays seen with unilateral stimulation.

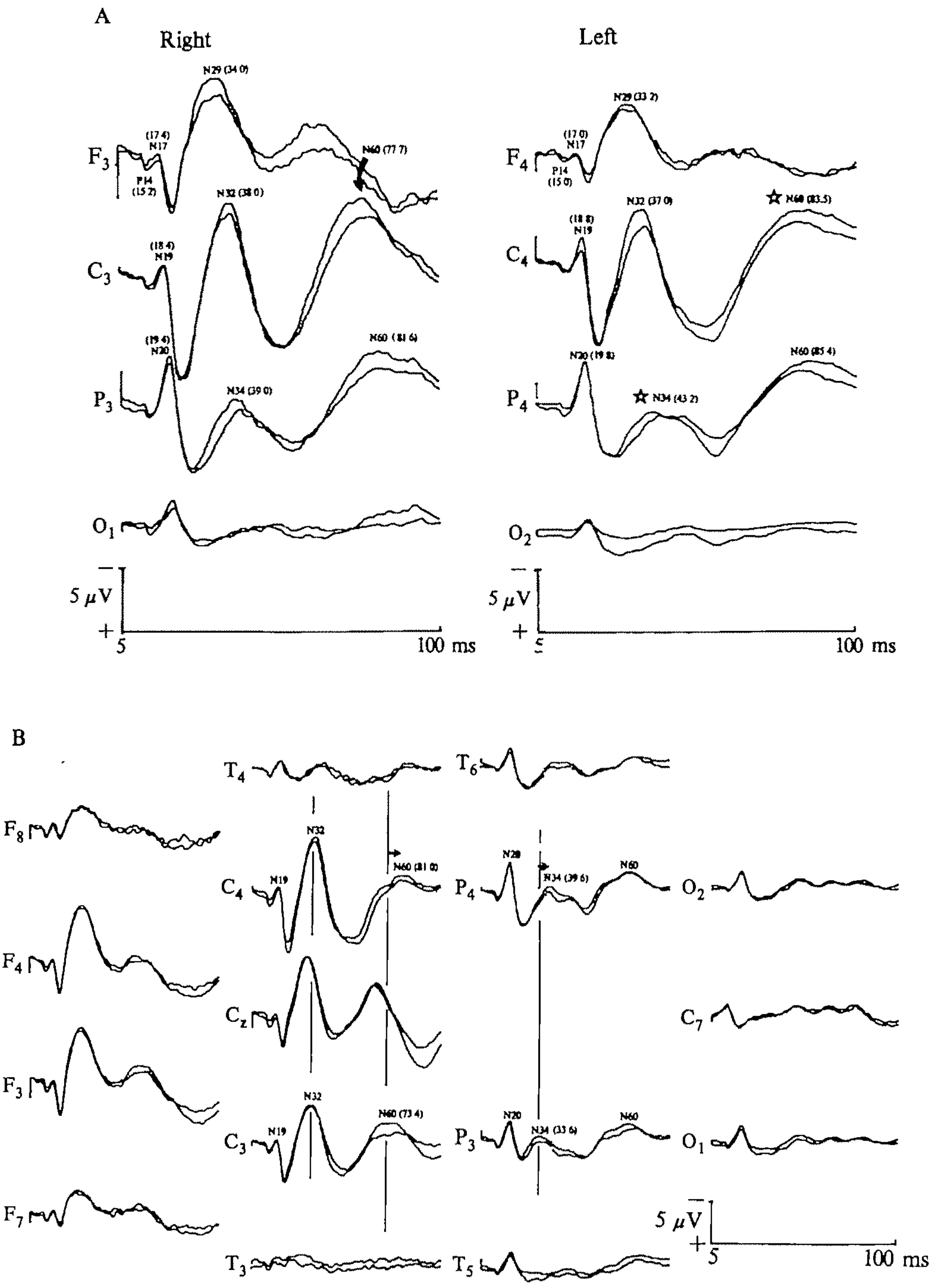

FIG. 10A. Right and left unilateral stimulation in *Case 15* showing a possible delay at N34 at P_4 and N60 at C_4 (open stars). N60 at P_4 may also be delayed. B, two trials of bilateral stimulation in *Case 15* which confirm the delays in N34 at P_4 and N60 at C_4 suspected with unilateral stimulation. However, the possible delay of N60 at P_4 could not be confirmed.

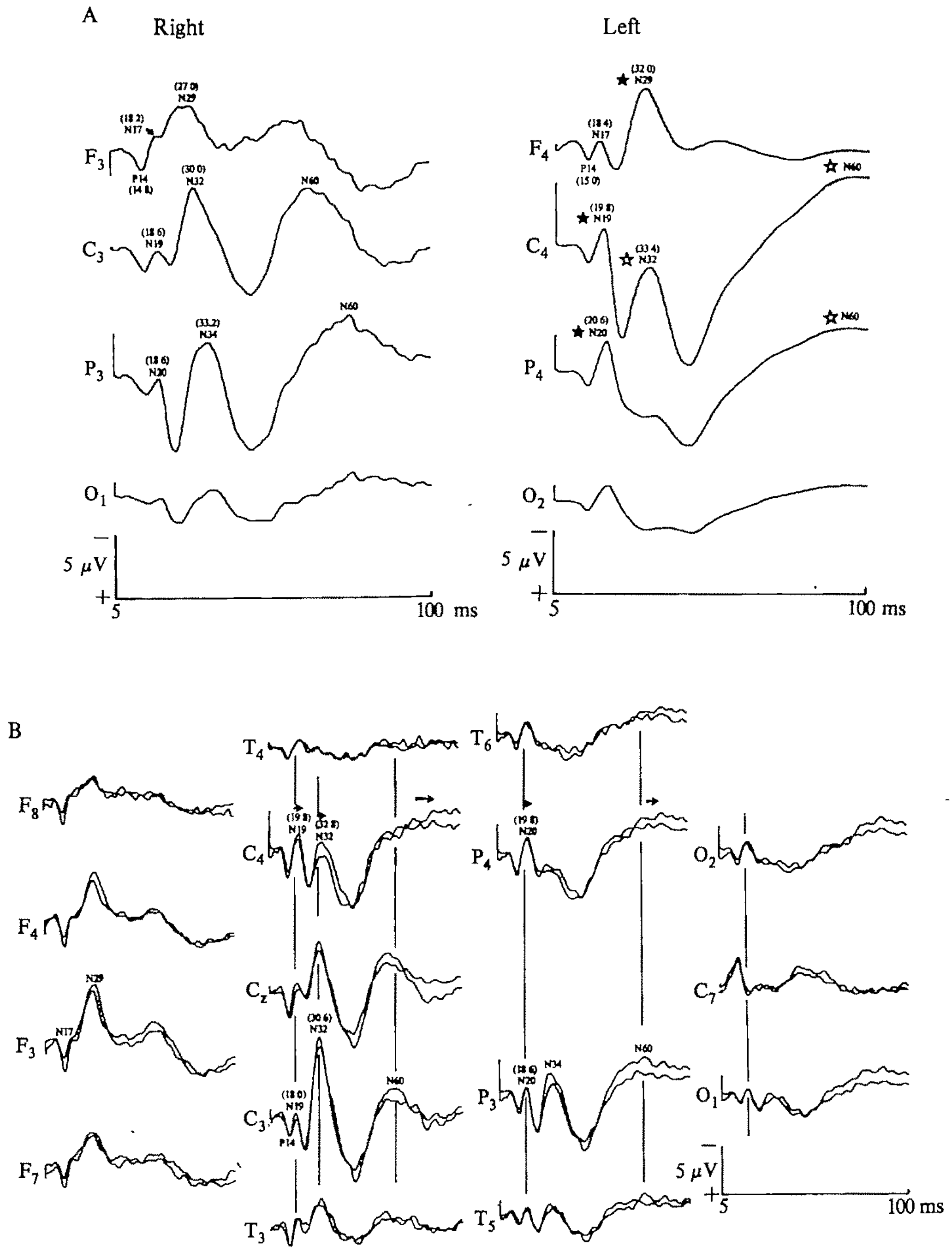

FIG 11A. Right and left unilateral stimulation in *Case 18* showing normal evoked responses over the left hemisphere and a delay in N19, N20 and N29 (black star), and a possible delay in N32 and N60. In contrast to *Case 10* (fig. 9A, B) note that N17 is not delayed. B, two trials of bilateral stimulation which confirm the delays at N19, N20, N32 and N60.

Anatomical Findings

The *geniculothalamic artery* is a branch of the posterior cerebral artery and is often occluded with posterior cerebral occlusion (Goto *et al.*, 1979). We have seen 11 patients whom we believe have had infarctions in this distribution; 9 had CT confirmation while 2 had negative CTs. The latter can be explained by the timing of CTs which were performed at a time interval after the infarction when lesions may not be evident because of isodensity of the region of infarction. This point has been demonstrated with sequential CTs (Goto *et al.*, 1979). The SERs and clinical findings are so similar to our other CT-confirmed cases that we think it is likely that there are similar lesions in the thalamus. There are other CT reports of lesions in this distribution with similar clinical findings (Goto *et al.*, 1979; Beasley *et al.*, 1980). There may or may not be concomitant posterior cerebral infarctions, depending upon the collateral circulation from the middle and anterior cerebral arteries (Goto *et al.*, 1979). The geniculothalamic artery commonly supplies the following thalamic nuclei: pulvinar, ventroposterolateral, ventroposteromedial, part of the centrum medianum and the medial geniculate (fig. 1B) and has also been reported to supply part of the following nuclei: dorsomedial, posterolateral, reticular, parafascicular and lateral geniculate (Schlesinger, 1976). An important point is that this artery supplies the primary sensory nuclei.

Thalamic lacunes with a 'pure hemisensory loss' are often not seen on CT (Fisher, 1982). Pathologically they are situated in the primary sensory nuclei of the thalamus. We have demonstrated 5 such cases on CT and the location is the posterolateral thalamus but, as expected, the lesions are not as extensive as in complete geniculothalamic occlusion.

The *tuberothalamic artery* is a branch of the posterior communicating artery. We have now seen 5 patients with thalamic lesions in this distribution. Two of our cases suffered thalamic infarction after clipping of giant posterior communicating artery aneurysms. The CT appearance was typical of this group. This supports the idea that occlusion of the tuberothalamic artery, a branch of the posterior communicating artery, may cause infarction in the anterolateral quadrant of the thalamus.

Archer *et al.* (1981), using CT with sagittal reconstruction and the Schaltenbrand and Wahren Atlas (1977), listed the nuclei destroyed in a case with an anterolateral thalamic infarction. There was an excellent overlap between Schlesinger's (1976) definition of the nuclei that should be supplied by the tuberothalamic artery and the findings of Archer *et al.* as to the actual nuclei involved in the thalamic infarction they studied. Our 5 patients with tuberothalamic infarctions had CT images similar to those in the case of Archer *et al.* (1981).

Further confirmation that we are dealing with tuberothalamic artery territory comes from the CT examination in patients who have undergone stereotactic ventrolateral thalamotomy (Murayama *et al.*, 1982). The ventrolateral thalamic nucleus (VL) is in the tuberothalamic arterial territory. Stereotactic lesions in VL have a similar (but less extensive) CT appearance to our tuberothalamic infarction group.

The deep *interpeduncular profunda artery* is a branch of the basilar root of the posterior cerebral artery. One artery may supply the medial thalamus bilaterally or unilaterally. Two of our patients in this group had bilateral medial thalamic infarctions. We have studied 1 patient with deep interpeduncular profunda artery occlusion by CT and subsequently at postmortem (Graff-Radford *et al.*, 1985). The CT showed the typical medial thalamic low densities. There have been other case reports with lesions in this location (Mills and Swanson, 1978; Smith and Laguna, 1981) and the CT findings are very similar to our cases.

Stereotactic thalamotomies for pain centred on the centrum medianum (a nucleus invariably supplied by this artery) caused a similar CT appearance to infarction in this arterial territory (Colombo *et al.*, 1981).

As the tuberothalamic artery may be small or even absent in certain patients (Lazorthes *et al.*, 1976), the interpeduncular profunda may supply the dorsomedial, ventrolateral and anteroventral thalamic nuclei and, in addition, has been described as supplying the dorsolateral, posterolateral, ventroposteromedial and ventroposterolateral thalamic nuclei (fig. 5B). In the majority of cases, part of the dorsomedial, centrum medianum, and parafascicular nuclei are its main territory of supply (Schlesinger, 1976; Castaigne *et al.*, 1981).

The posterior limb of the internal capsule is irrigated by the *anterior choroidal artery* (Lazorthes *et al.*, 1976). Takahashi *et al.* (1980) have demonstrated the CT findings of arteriographically proven anterior choroidal artery lesions. They wrote that the most vulnerable areas are the globus pallidus and the posterior limb of the internal capsule. Based on the CT analysis of our patients, we concur. The anterior choroidal artery territory, as depicted on CT templates, corresponds to the area of infarctions seen in Cases 18 to 25 (Damasio, 1983).

We have examined a 48-year-old woman who had her right anterior choroidal artery sacrificed during the clipping of a giant internal carotid/posterior communicating aneurysm. The resulting subcortical infarction involved the medial globus pallidus, posterior internal capsule and lateral thalamus. The location of the lesion in this verified case of anterior choroidal artery interruption helps to validate the interpretation we offer for other patients in the group who had infarctions in the same region.

The anterior choroidal artery supplies part of the amygdala, medial temporal lobe, globus pallidus, posterior limb of the internal capsule and lateral thalamus (Carpenter *et al.*, 1954; Schlesinger, 1976). The thalamic nuclei that have been reported to receive blood supply from the anterior choroidal artery are the lateral geniculate, reticular, pulvinar, and ventroposterolateral (Schlesinger, 1976) (fig. 6B).

Only 2 patients in this group had arteriography. One of them had an absent anterior choroidal artery and in the other the artery could not be traced beyond the plexal point. At this time we believe many of these lesions are due to occlusions of branches of the anterior choroidal artery. Some patients have complete anterior choroidal artery occlusion.

Clinical and Neuropsychological Findings

As noted, these different anatomical loci were associated with identifiable clinical and neuropsychological profiles.

Geniculothalamic infarction may cause the Dejerine-Roussy (1906) syndrome. Two of our patients with lesions in this territory had this syndrome and a third without CT confirmation also developed it. But the clinical hallmark of a lesion involving the complete geniculothalamic distribution is loss of sensation in all primary modalities. At present we do not know why some with lesions in this territory lead to dysaesthesia and some do not. There do not appear to be major cognitive deficits, aphasia, apraxia or amnesia associated with this type of lesion, although a few abnormalities can be found on more demanding neuropsychological tests such as copying of a complex figure and controlled oral word association. Concomitant posterior cerebral occlusion can be associated with a hemineglect syndrome and more extensive neuropsychological deficits.

A geniculothalamic lacune in the primary sensory nuclei causes the 'pure hemisensory loss'. We have found little or no neuropsychological deficit to accompany such lesion unless there is concomitant posterior cerebral artery occlusion.

We have described elsewhere the clinical presentation and neuropsychological profiles of the anterolateral thalamic group (Graff-Radford *et al.*, 1984). We now add another patient. These patients may have a hemiparesis and an emotional facial paresis but they do not usually have sensory deficits. In those with left-sided lesions, severe language deficits with aphasia are present (Graff-Radford and Damasio, 1984), along with marked decline in intellectual performance, visual perception, constructional praxis, memory and temporal orientation. Those with lesions on the right side have preserved verbal intellect, verbal memory, and speech and language. However, nonverbal intellect, visual perceptual discrimination, spatial judgement, visual memory for designs and constructional praxis are disturbed. Over a prolonged period the patients improve significantly but the pattern of deficits remains (Graff-Radford *et al.*, 1984). We believe that impairment in memory performance exhibited by this group may in part be secondary to their difficulties with language and visuospatial processing.

The medial thalamic group have no sensory or visual field deficit but may have a motor deficit. The latter could result from occlusion of a branch of the interpeduncular profundus artery to the cerebral peduncles. They also have vertical gaze paresis, probably related to infarction of the rostral part of the medial longitudinal fasciculus (Büttner-Ennever *et al.*, 1982). In the early stages of damage, intellect, memory, visuospatial processing and orientation are all affected in this group but no speech disturbance or aphasia is evident in our 3 cases. When these patients are followed clinically and with serial neuropsychological testing, amnesia becomes their main cause of disability as intellect, visual perception and spatial processing improve. The severity of the initial neuropsychological deficits may in part be secondary to attentional difficulties. The patients can be drowsy in the beginning with waxing and waning levels of attention. In the chronic phase, these patients could be described as having an amnestic syndrome.

For two years after her stroke we have followed Case 15 who had bilateral medial thalamic lesions, larger on the right than the left. She has continued to exhibit anterograde memory impairment, most clearly demonstrated by her impaired performances on the Rey Auditory Verbal Learning Test and recall of the Rey-Osterrieth Figure. Delayed recall (30 min) of the paragraph stories of the Wechsler Memory Scale was zero. These deficits were of clinical significance. Retrograde memory was also impaired. She scored 12 out of 48 on the Famous Faces portion of the Boston Remote Memory Test. Phonemic and semantic cues were of little help, but providing the first name to her led to improved recall. No temporal gradient of amnesia was evident.

We consider that this patient's amnesia was similar to Case A.V. (Butters, 1984) who had a thalamic tumour and both anterograde and retrograde amnesia components, the latter without temporal gradient. However, our Case 15 is different from Case H.M. (Scoville and Milner, 1957; Penfield and Milner, 1958) in that H.M.'s anterograde deficit was more severe and there was no retrograde component before the age of 16. In D.R.B. (Damasio *et al.*, 1985*a*), who suffered severe bilateral temporal lobe damage and basal forebrain damage due to herpes encephalitis, both the anterograde and retrograde components of memory are more impaired than in our Case 15. In cases of amnesia related to basal forebrain lesions (Damasio *et al.*, 1985*b*), both the anterograde and retrograde amnesia is usually less severe. N.A. (Squire and Moore, 1979), who had a stab wound through the nostrils up to the left medial thalamus, had less retrograde amnesia than this patient. Our patient exhibited some similarity to patients with Korsakoff's syndrome in that there were both anterograde and retrograde components to the amnesia. However, the lack of temporal gradient in the retrograde component of the amnesia is dissimilar to the Korsakoff's patient reported by some (Albert *et al.*, 1979), but not other researchers (Sanders and Warrington, 1971). Our evaluation of this patient's amnesia is based on the above-mentioned tests. A more extensive battery of tests may help further to characterize the amnesia.

All the patients in the lateral thalamus/posterior limb of internal capsule group had a hemiparesis. Some of these patients would previously have been classified as 'pure motor hemiparesis'. On detailed testing, however, a few had minor sensory deficits; one had a transient visual field deficit—the anterior choroidal does supply the optic tract and the lateral geniculate body partially. Most had some neuropsychological deficit. Although the left-sided lesions do not cause an aphasia, dysarthria is common and there can be mild language processing difficulties such as in controlled oral word association or reading comprehension of paragraphs. Assessment of short-term verbal and visual memory may reveal mild deficits in some cases, but these do not appear to be related to clinically significant amnesia. Patients usually have difficulty with short-term verbal memory tasks such as the Rey Auditory Verbal Learning and the Wechsler Memory Scale. It is possible that the mild language deficits exhibited by these patients may affect their verbal memory performance or *vice versa*. In addition, short-term visual memory testing (Benton Visual Retention Test and Recall of the Rey-Osterrieth Complex Figure) often falls in the defective range. This cannot easily be explained by a visuoperceptive disturbance because the patients usually perform well on tests of visual perception. The 2 cases with right-sided posterior limb/lateral thalamic lesions showed consistently defective visual perception, short-term visual memory for designs (perhaps secondary to the visuoperceptive disturbance) and nonverbal intellect performances. In contrast, language, short-term verbal memory and verbal intellectual abilities were normal.

It must be remembered that the anterior choroidal artery supplies part of the medial temporal lobe. Thus the mild memory deficits, even if they are not secondary to verbal and visual perceptual abnormalities, are not necessarily related to the thalamic component of the infarction.

Electrophysiological Findings

We found that a loss of both proprioception and pain sensation from thalamic infarction was indicative of a complete geniculothalamic infarction. This corresponded to an absence of SERs of all waves after P14 (i.e. N17, N19, N20, N29, N32, N34 and N60) when the affected hand was stimulated alone. In contrast, a lacune in the same arterial territory caused impaired pain sensation but preserved proprioception. This corresponded to an intact N17, N19 and N20, but a delayed or absent N32. It is tempting to conclude that N19 reflects the medial lemniscus (proprioception) pathway and N32 the spinothalamic (pain) pathways, but with so few cases this conclusion is not well founded. A more general observation is that a partial lesion in the primary sensory nuclei (VPL and VPM) affects pain sensation and may correlate with N32 delay, whereas a complete lesion affects all modalities of sensation and correlates with a unilateral absence of all evoked responses after P14.

Waves N17, N19 and N20 probably reflect sensory pathways (Ervin and Mark, 1964; Celesia, 1979). It is reasonable to ask why these waves are delayed in tuberothalamic infarction when the primary sensory nuclei are preserved and sensation is intact. We believe this may reflect a disturbance of the gating mechanism from destruction of part of the reticular nucleus of the thalamus, a nucleus irrigated in part by the tuberothalamic artery (Schlesinger, 1976). Yingling and Skinner (1977) have shown in the cat that stimulating the inferior thalamic peduncle to the frontal lobe or the reticular nucleus situated anterior to the ventroanterior thalamic nucleus diminishes sensory evoked potentials in visual, auditory and tactile modalities by interfering with the gating mechanism. Thus damage in this area may be the reason for the abnormal SERs. The lateral thalamic/posterior capsule group may also show a delay of N19, N20, N32 and N34 with minimal sensory deficit. Again, it is possible that the thalamic reticular nucleus is involved, this time adjacent to VPL and VPM, supporting the idea that SER delays can result from disturbed gating secondary to thalamic reticular nucleus destruction. Skinner and Yingling

(1977) also showed that, in the cat, stimulation of the reticular nucleus adjacent to VPL causes a delay in SERs in the tactile modality only.

N17 is recorded bifrontally with unilateral median nerve stimulation, suggesting a central origin of this wave. Others have also reported this wave (Abbruzzese *et al.*, 1978; Desmedt and Cheron, 1981; Eisen, 1982; Mauguière *et al.*, 1983). It is the earliest wave to be affected in the patients with geniculothalamic infarction, possibly indicating that it originates in the primary sensory nuclei (VPL and VPM). This is supported by direct recording in the primary sensory thalamic nuclei which shows a wave of a similar latency, 17.5 ms (Fukushima *et al.*, 1976) and 17 ms (Ervin and Mark, 1964). Simultaneous recordings in the thalamus and over the postcentral gyrus show that the cortically recorded wave is 2 ms later than that in the thalamus (Celesia, 1979). The origin of N19 is a source of controversy. Some attribute it to the thalamus (Goldie *et al.*, 1981; Chiappa and Ropper, 1982) and others to thalamocortical pathways or cortex (Allison *et al.*, 1980; Mauguière *et al.*, 1982). If N17 is thalamic, which seems possible from the above data, then N19 is likely to be generated more distally in the thalamocortical pathway or in the cortex itself.

We believe that it is important to record in frontal, central and parietal scalp regions with unipolar electrodes. As can be appreciated from our data, we have noted dissociations between waves recorded at these areas with the thalamic infarctions. For example, we have seen a normal N17 response in the frontal region but delayed N19 and N20 in the central and parietal areas (Case 18) or a delay in N32 at the central area but a normal N29 and N34 in the frontal and parietal regions (Case 20). Because of these dissociations and because the latencies recorded in the different scalp areas are consistently different, we believe that the origin of the waves recorded at various scalp areas is probably different. Most importantly, from a clinical standpoint, by recording in frontal, central and parietal areas, and by obtaining the patterns of SER abnormalities caused by different thalamic lesions, we are able to use the SER as a diagnostic aid in documenting and localizing lesions. Thus, in 2 cases, patients had normal CTs but distinctive SER patterns. In 1 case, the patient had a thalamic pain syndrome and absent SERs after P14. This corresponded to the posterolateral thalamic infarction group. As mentioned earlier, Goto *et al.* (1979) have shown with serial CTs in posterolateral thalamic infarction that the infarction may 'apparently disappear' from the CT scan, which may explain our not seeing this lesion on CT. In the other case, a unilateral loss of response to pinprick corresponded to a contralateral delay in N32 and N34. Fisher (1978) has also reported that patients with pure hemisensory loss may have normal CT scans. In these 2 cases the somatosensory evoked responses were clinically useful in lesion localization.

Conclusions

The clinical, neuropsychological and physiological features that characterize each anatomically defined group are as follows.

1. Patients with complete geniculothalamic infarction usually have multiple

modality sensory loss, may have associated dysaesthesia, hemiparesis, hemianopia and choreiform movements. Neuropsychological evaluation reveals few abnormalities unless there is concomitant posterior cerebral infarction. With median nerve stimulation there is a complete absence of evoked responses after the brain-stem wave (P14) in the hemisphere ipsilateral to the lesion.

A partial geniculothalamic lesion causes contralateral sensory loss involving part of the body for the modalities of pain and light touch but not proprioception or vibration. Occasionally there may be dysaesthesia but there are no motor signs. There may be a visual field defect if there is concomitant posterior cerebral infarction. Neuropsychologically there are few deficits unless there is posterior cerebral infarction. The most common somatosensory evoked response pattern is delay of the N32, N34 and N60 waves with normal N17, N19 and N20 responses.

2. Tuberothalamic infarction is often associated with facial paresis for emotional movement. Sometimes there is also a hemiparesis and visual field defect. Only rarely is there sensory loss. This group is severely impaired on neuropsychological evaluation with intellect, speech, language, all spheres of memory, visual perception and orientation all being affected with left-sided lesions. In contrast, right-sided lesions spare verbal intellect, speech, language and short-term verbal memory. The intellectual, perceptual, constructional and language defects improve, but a similar pattern of impairment remains. These patients often show a delay in N17, N19 and N20 as well as the later waves. Such abnormalities may also improve.

3. Interpeduncular profundus infarction often causes drowsiness in the early stages. Commonly there is supranuclear vertical gaze paresis and, on occasion, hemiparesis. These patients initially have significant cognitive impairment, especially affecting attention span, orientation, intellect, memory and visual perception, but language is preserved. Improvement is the rule, although the residual amnesic syndrome with anterograde and retrograde components may persist. Following median nerve stimulation there is often a delay in the N60 with preservation of the earlier waves.

4. Anterior choroidal infarction almost invariably causes a contralateral hemiparesis. Sometimes there is sensory loss for pinprick or light touch, but not proprioception or vibration. Dysarthria is common. Occasionally there is a visual field defect. Neuropsychological testing reveals that about half of the cases with left-sided lesions may exhibit mild deficiencies in memory and controlled oral word association, but aphasia, apraxia and amnesia are not evident. Right-sided lesions, on the other hand, most often affect only aspects of visual perception and visual memory for designs. Intellect, verbal memory and language are usually well preserved. Sensory evoked responses are variable. N60 is commonly delayed, however.

Our findings indicate that when patients with nonhaemorrhagic thalamic infarctions are grouped according to the location of their lesions, as depicted by CT, the profiles of clinical, neuropsychological and somatosensory evoked responses reveal fairly consistent and identifiable symptom clusters. The recognition of these clusters may assist neurologists in the assessment of such patients, and may contribute to the understanding of these complex subcortical structures. But our findings must be tempered by the knowledge that arterial territories are subject to some variation. The complete validation of our results must await further post-mortem evaluations.

ACKNOWLEDGEMENTS

Supported by Program Project Grant POI NS 19632-01 from NINCDS. We acknowledge Steven Cornell for help with obtaining CT images. We thank Frank Sindelar for his drawings of thalamic arterial territories and Jean Hulme for assistance in the preparation of this paper.

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(*Received July 12, 1984. Revised October 11, 1984. Accepted November 6, 1984*)

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APPENDIX

NEUROPSYCHOLOGICAL DATA

Case No	*Age/sex*	*Years educ*	*Side of lesion*	*Date of stroke*	*Date tested*	*Temp. Orient*	*Verbal IQ*	*Perf IQ*	*MAE naming*	*MAE repetition*	*MAE Token Test*	*BDAE Reading S and P*
Maximum scores						−113	145	145	60	14	44	10
Posterolateral thalamic infarction												
1	48/F	10	R+	21 10 82	28 10 82	−8*	78*	57*		12		
2	78/F	—	R+	27 10 82	—							
3	64/F	12	R	03 03 83	08 03 83	−1	116	109	60	12	44	
4	58/F	12	R	18 06 83	28 06 83	0	106	99	56	13		
5	66/M	16	R	06 06 80	13 06 80						44	
					25 01 84	0	117	95*				
6	19/M	13	R	21 03 83	30 03 83	0	103	98	50	14		
					12 04 83	0	103	84*				
7	69/M	16	R+	03 01 80	16 02 84	0	120	87*				
8	65/M	16	L	09 03 83								
9	60/M	11	L+	23 10 83	05 02 84	−1	89	88				8
					21 06 84	0						
Anterolateral thalamic infarction												
10	67/M	12	L	08 04 82	13 04 82	−104*	67*	71*	18*	13	0*	5*
					29 08 82	−81*	86*	84*	36*	13	30*	6*
					22 05 84	−26*			44*	15	42	8
11	75/M	12	L	03 03 82	02 06 82	−61*	69*	75*	32*	13	23*	0
					31 08 82	−25*			16*	10	15*	7*
					18 07 83	−1	94	95	26*	12	40	7*
12	66/F	7	L+	03 04 78	25 04 78	−36*			22*	15		
13	67/F	8	R	26 08 82	02 09 82	−1	100	76*	58	15	43	10
					16 08 83	0	102	104				
14	60/F	8	R	19 08 83	09 09.83	0	106	76*				
					24 10 83				58	16	43	10
					01 11 83	0	97	78*				10
Medial thalamic infarction												
15	69/F	16	BLT	21 06 82	28 06 82	−102*	99*	75*	50	11	40	9
					17 02 84	−79*	117	93				
16	74/F	12	R	06 05 82	19 10 82	−102*	78*	61*		11		
17	81/M	12	BLT	31 01 82	09 02 84	−1	81*	65*	46	11	38*	9
					28 06 84	−1	93	77*				
Lateral thalamic/posterior limb of internal capsule infarction												
18	58/M	12	R	13 11 81	18 11 81	0	95	87				
19	63/F	12	R	01 06 83	10 06 83	−2	106	80*	58			
20	72/M	8	L	12 04 83	15 04 83	−8*	81	87	50	10	25*	
					14 09 83	0	84	81	50		41	9
21	47/M	12	L	12 04 80	12 05 80	0	111	112	56	11		
					19 08 82	0	104	103				9
22	67/M	8	L	24 08 81	28.08 81	0	104	114	56	12		
					03 12 82	0	106	114			41	
23	58/M	12	L	01 07 82	15 07 82	0	93*	88*	60	12	41	7
					13.06 83	0	110	109				10
24	62/F	9	L	02 08 83	05 08 83	−1	84	87	60	14	41	
					09 04 84	−2						
25	67/M	12	L	31 08 81	02 02 82	−2	92	87	54	11		
					06 07 82	0	91	82	58	12	44	

+ = Concomitant posterior cerebral artery cerebral infarct, * scores judged to be abnormal based on available norms as well as each patient's personal history, educational level, vocational background

Abbreviations Temp Orient = Temporal Orientation Test, Verbal IQ = Wechsler Verbal Intelligence Quotient, Perf IQ = Wechsler Performance Intelligence Quotient, MAE = Multilingual Aphasia Examination, BDAE Reading S and P = Boston Diagnostic Aphasia Examination, reading of sentences and paragraphs, COWA = Controlled Oral Word Association of Multilingual Aphasia Examination, WMS = Wechsler Memory Scale, Ment Cont = Mental Control subtest of Wechsler Memory Scale (WMS), Parag = Logical Memory (WMS), Paired Assoc = Paired Associate Learning (WMS), Rey AVLT = Rey Auditory Verbal Learning Test (1st trial, 5th trial, recognition trial and delayed recall trial), BVRT (Corr Err) = Benton Visual Retention Test (correct errors), R-O Complex Figure = Rey-Osterrieth Complex Figure, BRMT Famous Faces = Benton Remote Memory Test of Famous Faces, FRT = Facial Recognition Test, JLO = Judgment of Line Orientation, 3D Blocks = Three Dimensional Block Construction

NEUROPSYCHOLOGICAL DATA (*cont*)

					Rey AVLT Trials (max. 15)				*BVRT*		*R-O Complex Fig*		*BRMT*			
MAE COWA	*WMS*	*Ment Cont*	*Parag*	*Paired Assoc*	*1st*	*5th*	*R*	*DR*	*Corr*	*Err*	*Drawing*	*Memory*	*Famous Faces*	*FRT*	*JLO*	*3D Blocks*
58	143								10	26+	36	36	48	54	30	29
21*				5 7*										0*		0*
37	122	13 2	9.9	11.3					8	5				48	25	29
22*	143	14 7	19 1	16 0					4*	9*	21*	4½*		42	26	
									4*	8*				47	25	29
29	120	13 4	11 4	14 4					7	5				47	25	
36	99	7 6*	11 9	12 2					8	2	36			49	27	
34	94	6 2*	10 7	13 0					7	4	36			49	20	
17*	143	11 2	15 7	15 5					5	9*	32			39*	28	
32	101	13 2	5 4*	9 5					3*	9*	36			50	29	
	116	10 4	12 9	10 2					10	0	34	24			29	
10*	57*	4 6*	5 8*	6 2*					2*	14*	15*			7*	10*	14*
10*	76*	7 9	12 4	8 0	2*	4*	6*	6*	4	11*			3*	38*	15*	29
25				7 7					4	7	29*	7*		39*		
10*	64*	5 8*	4 9*	5 8*							26*			27*	16*	8*
7*				4 6*	0*	0*	0*	0*	1*	23*			7*	49		27*
17*	99	12 0	10 3	7 8					3	12	36			43	30	
1*														31*		
38	129	11 2	19 0	13 7	5	7	11	10	3	13*	16*	8*	3*	37*	5*	22*
17*					4	12	15	13	6	6	34	19½		43	16*	
46	106	10 5	10 4	10 1					4	10*				35*		
				12 6					2*	10*				42	27	29
43	124	9 2	9 9	14 7	5	9	11	7	4	7	35	11½*				
17*	62*	10 1	5 2*	6 5*	0*	4*	3*	0*	1*	20*	21*	1*	8*	30*	17*	25*
41	101	14 8	10 9	9.2	5	6*	11	2*	4	11*	36	5*	12*	51		29
14*	62*	7 6	6 7*	5 4*	0*	5*	1*	1*						25*		6*
16*	79*	8 2	6.7*	7 4*					2*	17*	32			36*	5*	
24*	89	11 8	8 5	9 4					3	12				36*	19	
				8 0					3*	15*				44	2*	28
46	143	11 8	14 9	14.1	7	11	14	10	5	10*	28*	24		37*	25	29
15*	73	6 4	6 9	6 8	3	4*	5*	0*	3	17*	35	4*	19*	49		29
30	74	7 8	8.4	6 7	3	5*	5*	2*	3	13	24*	5*	22*			
	95	8.5	8 8	5 4*					8	2				43		
37	101	14 2	9 7	7 6	4*	10	12	4*	6	9*	33	19½	37	41	30	
26	93	9 0	11 3	10 4					4	7				45		
32	103	10 1	10 2	12 2	4	9	11	5	5	8	31	7*		47		29
18*	77*	12 8	6 1*	7 2*	4*	3*	4*	1*	2*	13*				44	21	29
29	108	14 7	11.1	11.1	3*	8	10	5*	4*	8*	35	11*				
33	95	7 6	8 4	8.8	6	6	12	4	3*	12*	22½*	13*		40	23	
41	92	6 2	7 4	10 2	4	7	13	7	3*	11*	33		3			
22*	93	12 3	8 5	8 0										43		
23*	94	9 0	9 1	11 0	3	5*	11	5						39*	24	29

SOMATOSENSORY EVOKED RESPONSES

Case No.	Date of Stroke Dy Mo Yr	Date of SER Dy Mo Yr	*N17(F)*	*N19(C)*	*N20(P)*	*N29(F)*	*N32(C)*	*N34(P)*	*N60(C)*	*N60(P)*
Posterolateral thalamic infarction										
1	21 10.82	04.11.82	ABS	ABS	ABS	ABS	ABS	ABS	ABS	ABS
2	27.10 82	03 11.82	ABS	ABS	ABS	ABS	ABS	ABS	ABS	ABS
3	03.03.83	09.03 83	ABS	ABS	ABS	ABS	ABS	ABS	ABS	ABS
4	18.06.83	24.06.83	ABS	ABS	ABS	ABS	ABS	ABS	ABS	ABS
5+	06 06 80	01 01 84	NML	NML	NML	NML	NML	NML	NML	NML
6	21 03 83	30 03 83	NML	NML	NML	DL	DL	DL	DL	DL
7	03.01 80	04.02.84	*	*	*	*	*	*	*	*
8	09 03 83	09 09 83	NML	NML	NML	DL	DL	DL	DL	DL
9	23.10.83	08 02.84	*	*	*	*	*	*	*	*
Anterolateral thalamic infarction										
10	08 04 82	26 05 82	DL	DL	DL	DL	DL	DL	DL	ABS
11	03.03.82	21.04 82	DL	DL	DL	DL	DL	DL	DL	NML
12	03.04 78		NA	NA	NA	NA	NA	NA	NA	NA
13	26 08.82	03 09 82	DL	DL	DL	NML	NML	NML	DL	*
14	19 08.83	30.08 83	NML	NML	NML	NML	NML	NML	DL	DL
Medial thalamic infarction										
15	21 06.82	30 06 82	NML	NML	NML	NML	NML	DL	NML	DL
16	06.05 82	11 10 82	NML	NML	NML	NML	NML	NML	DL	DL
17	31 01 82	09 02 84	NML	NML	NML	NML	NML	NML	DL	DL
Lateral thalamic/posterior limb of internal capsule infarctions										
18	13.11 81	11.11 81	NML	DL	DL	DL	DL	DL	DL	DL
19	01.06 83	07.06 83	NML	*	*	ABS	*	*	DL	DL
20	12.04.83	14 04.83	NML	NML	NML	NML	DL	NML	DL	DL
21	12.04.80		NA	NA	NA	NA	NA	NA	NA	NA
22	24 08 81	03 12 82	NML	NML	NML	NML	NML	NML	DL	DL
23	01 07 82	16.07 82	NML	*	*	DL	DL	DL	DL	DL
24	02 08 83	08.08.83	NML	NML	NML	NML	NML	NML	DL	DL
25	31 08.81	06 07 82	NML	NML	NML	NML	NML	NML	DL	DL

ABS = absent; DL = delay, NA = not available, NML = normal, * = uninterpretable, + = normal sensation arm, only leg has decreased sensation

Brain (1985), **108**, 517–533

SUBSTANCE P AND THE SENSORY INNERVATION OF INTRACRANIAL AND EXTRACRANIAL FELINE CEPHALIC ARTERIES

IMPLICATIONS FOR VASCULAR PAIN MECHANISMS IN MAN

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SUMMARY

Substance P, a putative neurotransmitter peptide present in a subpopulation of small sensory neurons, was measured in the walls of feline cranial arteries and systemic veins and arteries using a sensitive and specific radioimmunoassay. Substance P immunoreactivity exhibited a retention time identical to that of synthetic substance P when vessel extracts were subjected to reverse phase high performance liquid chromatography. Levels in cephalic arteries (453–1083 fmol/mg protein) were at least twice as high as amounts in systemic arteries and veins, and were significantly higher than those measured in the cornea and lip. Unilateral excision of the trigeminal ganglion decreased the peptide by 44 to 86 per cent in ipsilateral intracranial and extracranial arteries (e.g. external and internal maxillary, lingual, temporal, anterior, middle and posterior cerebral, superior cerebellar and posterior communicating arteries). Extracranial arteries were decreased on average by 78 per cent, whereas intracranial arteries were reduced by 55 per cent. Unilateral removal of the superior cervical sympathetic ganglion was without effect. The described pattern of sensory innervation provides a possible explanation for the referral of pain to the forehead and anterior scalp during attacks of migraine, and with arteritis and thrombosis involving vascular structures within the posterior fossa, the circle of Willis and the external carotid system of man.

INTRODUCTION

Nerve fibres are found in abundance within the adventitia of large pial arteries comprising the circle of Willis (Penfield, 1932; Humphreys, 1939; Nelson and Rennels, 1970; Dahl, 1973). Most are likely to be sympathetic or parasympathetic fibres although some are probably axons of primary afferent neurons (Burnstock *et al.*, 1970). Very little has been written about the sensory innervation of cerebral arteries. Hovelacque (1927) and Sheehan (Northfield, 1938) identified several fine branches between the trigeminal ganglia and internal carotid artery, but were

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uncertain as to whether the connections represented sympathetic fibres innervating trigeminal ganglia or *vice versa*. Penfield and McNaughton (1940) and Fang (1961) looked for and did not find nerve fibres joining the trigeminal ganglia and cerebral arteries. Suggestive evidence for such an innervation was provided by studies in which intracranial vessels were stimulated and an autonomic response, verbal report, or behavioural change was elicited. For example, Levine and Wolff (1932) showed that electrical stimulation over feline pial arteries increased the galvanic skin response, and that this response could be blocked by the application of procaine to the vessel surface. Wall and Pribram (1950) found that trigeminal neurotomy blocked the development of elevated systemic blood pressure during electrical stimulation of pial arteries in *Macacca mulatta*. In man, Fay (1932), Penfield and McNaughton (1940), and Ray and Wolff (1940) elicited pain during electrical stimulation of pial and dural arteries under local anaesthesia. Large pial arteries were most sensitive at their proximal ends and became progressively less so distally. A sensory innervation was also suggested by the ability of nociceptive substances such as bradykinin, serotonin or potassium, when injected into the internal carotid artery, to elevate blood pressure and produce vocalization and escape movements in animals (Guzman *et al.*, 1962).

Recent animal experiments from our laboratory provided the first anatomical evidence for the existence of sensory connections from the trigeminal nerve to the circle of Willis (Mayberg *et al.*, 1981). In these experiments, horseradish peroxidase (HRP) or wheat germ agglutinin was used to determine connectivity (Liu-Chen *et al.*, 1984*b*; Moskowitz *et al.*, 1983*b*). When applied to the proximal middle cerebral artery, tracer was observed in the ipsilateral first division. In addition, labelling was found in sympathetic neurons throughout both superior cervical ganglia as well as within cells of the sphenopalatine and otic ganglia and the walls of the rete mirabile (presumptive parasympathetic neurons) (Walters *et al.*, 1985). No HRP-containing cells were found in the ganglia of the seventh, ninth or tenth cranial nerves or the dorsal root ganglia corresponding to the upper cervical segments. A similar (but not identical) pattern was found for the middle meningeal artery and superior sagittal sinus.

The present study was undertaken to determine the sensory innervation of cerebral arteries and, more specifically, to examine the contributions of the trigeminal ganglia to the innervation of large cerebral arteries of the circle of Willis. The approach taken was to measure levels of substance P (SP) in individual cerebral arteries following specific nerve lesions. SP was chosen because it has been suggested as a neurotransmitter candidate in primary sensory neurons (Lembeck, 1953). For example: (1) it exists in small unmyelinated primary sensory nerve fibres concerned with pain transmission and in a population of small diameter nociceptive primary sensory neurons in dorsal root ganglia (Hökfelt *et al.*, 1975*a*, *b*), including those of the trigeminal ganglia (Cuello *et al.*, 1978); (2) it is located in nerve fibres terminating in spinal cord regions shown previously to contain endings for those fibres responding to noxious stimuli (laminae I and II of dorsal horn); (3) it is released into the spinal cord with stimuli sufficient to activate small diameter unmyelinated peripheral sensory fibres but not with lesser intensities of stimulation (Yaksh *et al.*, 1980); and (4) its iontophoretic application depolarizes neurons in posterior horn of spinal cord, some of which become activated by nociceptive stimuli (for review, *see* Nicoll *et al.*, 1980). Because the onset of SP-induced depolarization was delayed and sustained even after the period of peptide application, some have speculated that SP may act more as a neuromodulator than as a classical transmitter (for reviews, *see* Jessell, 1982, and Yaksh and Hammond, 1982). Despite such controversy, we focused experiments on the SP molecule because of its demonstrated existence in primary sensory nociceptive fibres and because experiments to date indicate that SP is present in adventitial nerve fibres (Chan-Palay, 1977; Edvinsson *et al.*, 1981; Furness *et al.*, 1982) and that the density of this innervation decreases ipsilaterally in feline cerebral vessels following unilateral trigeminal lesions (Liu-Chen *et al.*, 1983*c*). In this report we provide evidence that vessels of both the anterior and posterior circulation receive SP-containing projections from the trigeminal ganglia and that trigeminovascular fibres also invest extracranial cephalic arteries ipsilaterally. The significance of these findings for diseases associated with vascular pain (e.g. migraine) is discussed.

This work has been presented in preliminary form (Moskowitz *et al.*, 1983*c*; Norregaard *et al.*, 1983, Moskowitz and Barley, 1985).

MATERIAL AND METHODS

Substance P was purchased from Beckman Instruments Co., Palo Alto, CA, and $(^{125}\mathrm{I})$Tyr-SP from New England Nuclear Co., Boston, MA. All chemicals were of reagent or HPLC grade.

Tissue Homogenization and Assay

Animals were killed by an overdose of sodium pentobarbital. Blood vessels were removed from the intracranial and extracranial cephalic circulation using a Zeiss operating microscope. In normal cats, the arteries of the circle of Willis were each divided into two or three segments as follows: (1) the anterior cerebral into two segments corresponding to the proximal 1 cm and the adjacent 1-1.5 cm; (2) middle cerebral into three consecutive 1 cm segments; (3) the posterior cerebral into two segments each 1 cm in length; and (4) the superior cerebellar artery into two 0.8 cm segments.

Arteries were washed free of blood with 0.1 M phosphate buffered saline (pH 7.4) containing 10 mM magnesium chloride and cleaned of attached tissues with the aid of a dissecting microscope. Vessels were frozen on dry ice and kept at −70 °C until assay. Frozen tissues were allowed to thaw and were then homogenized in 2 N acetic acid containing 0.01 per cent mercaptoethanol by ground glass homogenizers. Samples were centrifuged, supernatants dried, resuspended and then assayed for SP as described previously, after an aliquot was removed for protein determination (Liu-Chen *et al.*, 1983*a*). The antisera F2 employed was raised in the New Zealand white rabbit and was a generous gift from Dr Susan E. Leeman (University of Massachusetts, Worcester). Details of the radioimmunoassay (RIA) and specifity of antisera were published previously (Mroz and Leeman, 1979; Liu-Chen *et al.*, 1983*a*). The limit of assay sensitivity was defined as the amount of SP needed to displace at least 10 per cent of the bound iodinated SP (2.5 ± 0.1 fmol/tube).

High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) was performed on a system incorporating dual pumps (Waters Associates, Model 6000A, Milford, MA), using a Model 660 Solvent programmer and Model 45 A Solvent Delivery System. A μ Bondapack C-18 reverse phase column (3.9 × 30 cm; Waters Associates), was used for reverse phase separation as described previously (Liu-Chen *et al.*, 1983*a*). Dried acid extracts of vessels were prepared for chromatography as described above, except that the extract was passed through a C-18 minicolumn (Sep-Pak, Waters Associates), eluted with acetonitrile, dried, and resuspended in mobile phase prior to injection. The mobile phase consisted of acetonitrile and 0.01 M potassium phosphate buffer (pH 4.1) containing 0.2 M NaCl. A linear gradient of acetonitrile (0–30%, 30 min, 1.5 ml/min, approximately 1500 psi) was followed by an isocratic elution (30% acetonitrile). Fractions were collected at 1 min intervals in tubes containing 0.1 per cent bovine serum albumin. Samples were dried and assayed for immunoreactive SP (ISP) by RIA as described.

Surgical Procedure

Cats weighing 3 to 5 kg were used in all experiments. They were anaesthetized by intraperitoneal (i.p.) injections of ketamine hydrochloride (25 mg/kg) and sodium pentobarbital (10 mg/kg), intubated and allowed to breathe atmospheric air. Half an hour before surgery, bicillin 500000 IU, i.m. and gentamycin 4 mg i.p., were given. Gentamycin was repeated 8 and 16 h later and bicillin 16 h after the initial injection. All surgical procedures were performed under sterile conditions using an operating microscope and microsurgical technique.

Trigeminal ganglionectomy. The head of the cat was positioned in a specially designed headholder. Through a temporoparietal incision, the temporalis muscle was exposed, the anterior portion separated from the skull and lateral orbital fascia and transected anteromedial to the zygomatic arch. Using a dental drill and rongeurs, a temporal craniectomy was performed, Meckel's cave exposed and opened by an extradural approach and the cranial aspects of V2, V3 and the trigeminal root dissected. Subsequently V3 was cut at the level of the foramen ovale and the root cut posteriorly at the apex of the petrous bone. The inferior aspects of the ganglion were dissected and V2 was cut at the level of the foramen rotundum. The ganglion was then pulled laterally, exposing V1, which was dissected and cut at the point where it leaves Meckel's cave. The temporalis muscle was reattached to the lateral orbital rim and zygomatic arch and the superficial fascia and skin closed. An ipsilateral tarsorrhaphy was performed to prevent keratitis in the deafferented eye. At time of killing the cats were tested for sensation in the cutaneus distribution of the trigeminal nerve.

Unilateral or bilateral superior cervical sympathectomy (*excision of the superior cervical ganglion*). Cats were positioned in a supine position with the neck extended. Through an anterior longitudinal midline incision the neurovascular bundle was exposed on one or both sides. The sympathetic trunk, located just posteromedial to the vagus nerve, was followed cranially to the superior cervical ganglion, located inferomedial to the nodose ganglion. The sympathetic ganglion was dissected and excized. Fascia and skin were closed in layers. All animals were observed for miosis and paralysis of the nictitating membrane.

The cats were killed 14 to 20 days later. The brains were removed and individual vessel segments of the circle of Willis and branching vessels were dissected and frozen on dry ice. Whole vessels were assayed for SP to obtain levels above the sensitivity of the assay on the lesioned side. Vessels in fig. 2 and Tables 1–3 correspond to the following: the proximal segments of the anterior (2 cm), middle (3 cm) and posterior cerebral (2 cm), superior cerebellar (1.5 cm) and anterior inferior cerebellar (1.5 cm) arteries; the entire intracranial length of the internal carotid artery, the basilar arteries, and the intrathecal portion of the vertebral arteries; the common carotid artery from the level of the cricoid cartilage to the origin of the vestigial internal carotid artery; the proximal segments of the lingual (3 cm), external maxillary (2.5 cm), and internal maxillary (1.5 cm), and the distal superficial temporal (2 cm) arteries. All tissues were kept at −70 °C until assay.

Data are expressed as fmol SP per mg protein. Following unilateral trigeminal or superior cervical ganglionectomy, SP levels in blood vessels on the lesioned side were compared with identical segments on the unoperated control side. Student's t test was used for statistical comparisons.

RESULTS

Levels of SP were measurable in extracts of cerebral arteries composing the circle of Willis and ranged from 518 fmol/mg protein for the internal carotid artery to 1083 fmol/mg protein for the distal segment of the posterior cerebral artery (fig. 1). Levels were approximately 10-fold higher than those measured in pia-arachnoid containing these vessels (81 ± 10, n = 13), and were 30, 40 and 60-fold greater when compared with levels in skin, cornea and muscle, respectively (Table 1). Levels in intracranial cephalic arteries were in general four times those found in systemic arteries, and levels in systemic veins were in general lower than in the corresponding artery (Table 1). Extracranial cephalic arteries contained levels which were approximately two-thirds those found within the circle of Willis. Levels in cerebral arteries varied significantly between animals (*note* large SEM values, fig. 1), but with few exceptions, did not differ significantly between vessels. No differences were detected between vessels supplying the left or right side of the brain. In general, low levels in one vessel were accompanied by relatively low levels in all vessels from that

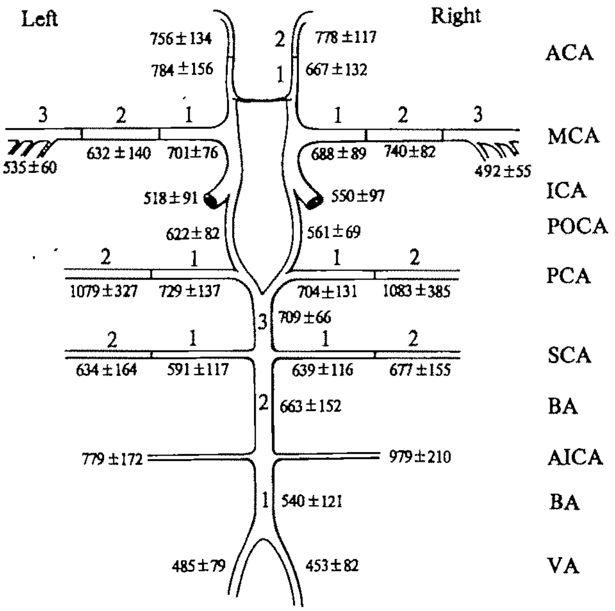

FIG. 1. Substance P levels (fm/mg protein) in feline cerebral blood vessels from the circle of Willis. Vessel segments from cats were dissected and assayed as described in the text. Values represent the mean ± SEM from 8 animals. Abbreviations for arteries are as follows. ACA = anterior cerebral; MCA = middle cerebral; ICA = internal carotid; POCA = posterior communicating; PCA = posterior cerebral; SCA = superior cerebellar; BA = basilar; AICA = anterior inferior cerebellar; VA = vertebral.

TABLE 1. LEVELS OF ISP* IN FELINE BLOOD VESSELS AND OTHER TISSUES

	fmol/mg protein
Cephalic arteries	
Superficial temporal (5)	365 ± 68
Lingual (4)	472 ± 103
Internal maxillary (4)	441 ± 75
External maxillary (4)	361 ± 48
Middle cerebral (8)	701 ± 76
Anterior cerebral (8)	784 ± 156
Posterior cerebral (8)	704 ± 131
Systemic arteries	
Femoral (5)	30 ± 13
Brachial (5)	35 ± 8
Abdominal (5)	26 ± 4
Pulmonary (5)	26 ± 10
Renal (4)	67 ± 13
Systemic veins	
Femoral (5)	21 ± 5
Cephalic (3)	37 ± 10
Inferior vena cava (5)	21 ± 9
Pulmonary vein (3)	40 ± 12
Renal vein (3)	34 ± 5
Skin (7)	12 ± 5
Muscle (4)	3 ± 1
Dorsal spinal cord (7)	798 ± 141
Cornea (15)	15 ± 4

*ISP = immunoreactive substance P. Dorsal spinal cord was taken from midcervical cord; skin from dorsal neck. Cephalic arteries were dissected and assayed as described in the text. Values represent the mean ± SEM. Number of specimens is indicated in parenthesis.

same animal. No differences were detected between arteries of the anterior and middle fossa (anterior, middle, posterior communicating and posterior cerebral arteries) and those of the posterior fossa (superior cerebellar, basilar and anterior inferior cerebellar arteries). The vertebral arteries contained lower SP values than other cerebral arteries, although these differences were not apparent in a subsequent series of animals (fig. 3). SP concentrations in the distal middle cerebral artery were significantly lower than in proximal segments. None of the other pial vessels showed this pattern, and levels in distal arteries were either similar or significantly higher (e.g. posterior cerebral artery) (fig. 1).

When extracts of cerebral arteries were separated and analysed by HPLC and RIA, the immunoreactive peaks exhibited retention times identical to that of both synthetic SP and of SP sulphoxide (fig. 2). Approximately 80 per cent of the injected immunoreactivity was recovered from the column and no additional peaks were detected. The specified chromatographic conditions were adequate to resolve

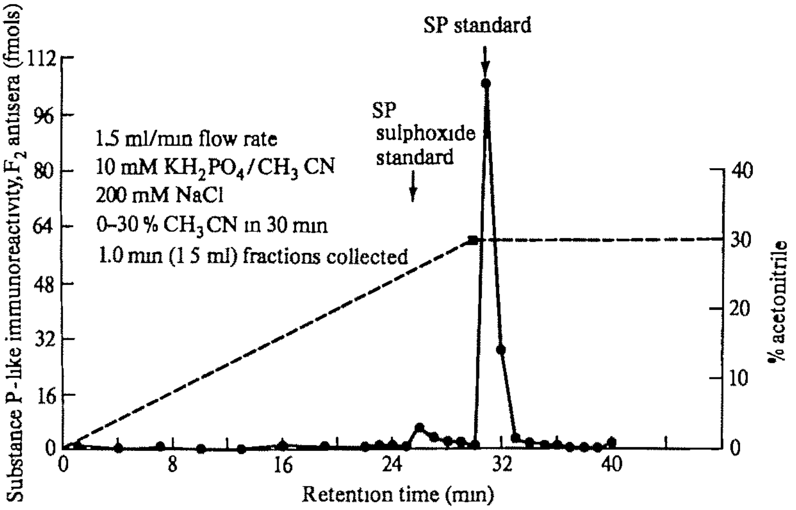

FIG. 2. High performance liquid chromatogram of feline pia-arachnoid containing cerebral blood vessels. Arrows indicate the retention times for standards of substance P and its sulphoxide derivative. Mobile phase and chromatographic conditions are indicated.

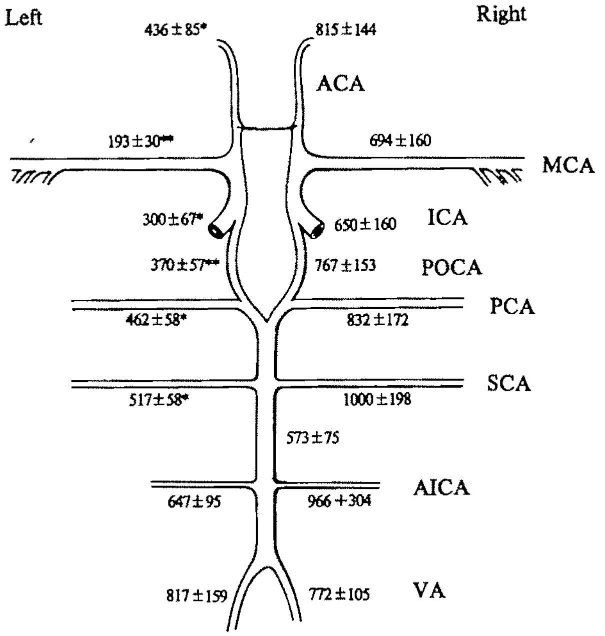

FIG. 3. Substance P levels in feline circle of Willis following left trigeminal ganglionectomy. Vessels were dissected and assayed as described in the text. Abbreviations as in fig. 1. Data are expressed as fm/mg protein and represent the means ± SEM Values for the posterior cerebral artery and vessels of the posterior fossa were obtained from 10 cats. Data from 6 cats were used to calculate values for the vessels of the middle and anterior fossae. *$P < 0.05$, **$P < 0.01$ as compared to contralateral paired vessel.

eleidosin but not physalaemin from SP. The cross-reactivity of the antisera was less than 1 per cent for both tachykinins.

All cats tolerated the surgical procedures well without wound or systemic infections. Following excision of the left trigeminal ganglion, cats were anaesthetic to touch and to the effects of bipolar coagulation on the forehead and face. This area of anaesthesia extended 3 cm above the left eye to the inferior margin of the mandible on that side. No corneal reflex could be elicited. Excision of the trigeminal ganglion significantly depleted SP in the following ipsilateral cerebral arteries: anterior, middle cerebral, internal carotid, posterior communicating and posterior cerebral arteries (fig. 3). Depletions ranged between 44 and 72 per cent, the middle cerebral artery showing the greatest depletion. Levels decreased by 49 per cent in the superior cerebellar artery ipsilaterally although the absolute SP levels were increased on the intact side by 150 per cent as compared with unoperated controls. None of the other SP values from the unoperated side differed from normal cats. These results are supported by immunohistochemical studies showing ipsilateral decreases in the number of immunoreactive cholecystokinin-8 axons in the superior cerebellar artery following unilateral trigeminal lesions (Liu-Chen *et al.*, 1984*a*). We have no explanation for the apparent increases measured in the superior cerebellar artery in the present study. In the extracranial circulation, depletions of 85 to 86 per cent were observed ipsilaterally in the superficial temporal, external and internal maxillary arteries. SP levels decreased in the lingual artery by 78 per cent. In 1 of the 4 cats, the lingual artery did not show a depletion and is not included in Table 3. By contrast, levels did not decrease significantly in the common carotid artery (Table 2).

Following excision of the superior cervical ganglion, all animals exhibited miosis and paralysis of the nictitating membrane. Two cats killed three weeks (but not two

TABLE 2 LEVELS OF ISP IN FELINE CEREBRAL ARTERIES FOLLOWING EXCISION OF RIGHT SUPERIOR CERVICAL GANGLION

	fmol/mg protein	
	Right	*Left*
Anterior cerebral	1115 ± 195	926 ± 141
Middle cerebral	470 ± 152	762 ± 288
Internal carotid	646 ± 147	691 ± 153
Posterior communicating	790 ± 238	856 ± 262
Posterior cerebral	774 ± 179	827 ± 239
Superior cerebellar	798 ± 255	622 ± 133
Anterior inferior cerebellar	885 ± 151	716 ± 160
Vertebral	761 ± 275	666 ± 135
Basilar	940 ± 352	
Trigeminal ganglion	608 ± 141	343 ± 88*

Vessel segments and trigeminal ganglia from 4 animals were dissected and assayed as described in the text. n = 4 for all blood vessels. * $P < 0.05$ as compared with right side.

TABLE 3. ISP LEVELS IN EXTRACRANIAL CEPHALIC ARTERIES FOLLOWING UNILATERAL TRIGEMINAL GANGLIONECTOMY

	fmol/mg protein		
Vessel	*Right*	*Left*	*% decrease*
Internal maxillary	441 ± 75	$61 \pm 36^*$	86
External maxillary	361 ± 48	$50 \pm 18^*$	86
Superficial temporal	382 ± 91	$67 \pm 32^{**}$	82
Lingual	326 ± 56	$72 \pm 19^{**}$	78
Common carotid	32 ± 16	$22 \pm 9^{\text{n.s.}}$	31

Vessel segments from 4 animals were dissected and assayed as described in the text. $^*P < 0.01$. $^{**}P < 0.05$ as compared with unoperated right side.

weeks) after surgery showed some disappearance of their sympathetic deficits (*see* Brodal, 1981). No depletions were observed on the sympathectomized side in any of the 4 animals and levels on the side contralateral to the lesion did not differ significantly from normal values (Table 3). SP levels increased significantly in the ipsilateral trigeminal ganglion following unilateral excision of the superior sympathetic ganglion. This was reported to occur in trigeminal axons innervating the iris following removal of the superior cervical ganglia (Kessler *et al.*, 1983).

DISCUSSION

The present studies were undertaken in order to investigate the relationship first postulated in 1979 between the trigeminal nerve, SP and cerebral arteries (Moskowitz *et al.*, 1979). In this report, we confirmed the existence of SP in trigeminal nerve fibres surrounding cerebral arteries. We established the authenticity of immunoreactive SP in feline cerebral arteries by reverse-phase HPLC. We determined that the trigeminal nerve provides the major source of SP in cerebral arteries and demonstrated that ipsilateral trigeminovascular fibres also projected to extracranial cephalic arteries.

The residual peptide in vessels from animals with trigeminal lesions may reflect subtotal ganglionic destruction, or it may derive from other neuronal projections. Possible sources are as follows. (1) The superior cervical ganglia, known to innervate cerebral arteries and to contain SP in cell bodies (at least in cell culture) (Kessler *et al.*, 1981). This is unlikely because SP levels did not decrease after sympathetic ganglionectomy (Table 3) or 6-hydroxydopamine treatment (Liu-Chen and Moskowitz, 1985). (2) Intrinsic brain neurons, shown previously to project to cerebral arteries from the raphe nucleus (Reinhard *et al.*, 1979), locus coeruleus (Hartman *et al.*, 1972), and cortical grey matter (Hendry *et al.*, 1983). (3) The contralateral fifth cranial nerve. Significantly greater lesion-induced depletions were found in arteries directed away from the midsagittal plane, and ipsilateral arteries of the circle of Willis receive bilateral sympathetic projections (Sato *et al.*, 1980). Also, results from retrograde tracing studies show that the middle cerebral and middle meningeal arteries are innervated by ipsilateral trigeminal neurons whereas the superior sagittal sinus may be innervated by trigeminal neurons from both sides (Mayberg *et al.*, 1984). (4) The upper cervical dorsal root ganglia. Because their target tissues refer pain to the occiput when stimulated, these ganglia might be expected to innervate at least the vessels of the posterior fossa. (5) The vagus nerve, a rich source of SP (Gamse *et al.*, 1979), was implicated as a possible source in several clinical reports that studied the vascular innervation within the posterior fossa (Fay, 1932; Ray and Wolff, 1940).

The existence of SP in afferent fibres raises important questions as to its fate and function. Its presence in vascular structures which are insensitive (e.g. convexity vessels, at least in man; Ray and Wolff, 1940) suggests other functions besides transmission of nociceptive information. Release of SP was demonstrated from peripheral axons surrounding blood vessels by potassium (at least 20 nM) and capsaicin by calcium-dependent mechanisms (Moskowitz *et al.*, 1983*a*). *In vivo* release is thought to account for the observed increases in blood flow and vascular permeability following antidromic stimulation, or chemically-induced inflammation (Jancsó *et al.*, 1968, 1980) in the eye (Bill *et al.*, 1979), nasal mucosa (Lundblad *et al.*, 1983), dental pulp (Olgart *et al.*, 1977), trachea (Lundberg and Saria, 1982) and skin (Lembeck and Holzer, 1979). Similar responses were also elicited by infusing SP (Saria *et al.*, 1983) or capsaicin (which releases SP during acute administration). The effects of SP were blocked by treatment with SP antagonists (Holmdahl *et al.*, 1981; Rosell *et al.*, 1981; Lembeck *et al.*, 1982), or by prior depletion of SP by deafferentation or pretreatment with capsaicin (Jancsó *et al.*, 1967). SP also degranulates mast cells (Johnson and Erdős, 1973) and antihistamines block some of the changes in skin caused by the application of SP (Lembeck and Holzer, 1979). SP also modulates the activity at, for example, beta-adrenergic receptors (Rougon *et al.*, 1983), and by analogy may modulate the activity of adjacent perivascular sympathetic and parasympathetic axons. It should not be surprising that neuroinflammation was suggested as a pathophysiological basis for some migrainous headaches (Moskowitz, 1984). Wolff showed that sterile inflammation developed in the walls of involved vessels (Ostfeld *et al.*, 1955). Others reported on the utility of anti-inflammatory drugs in the treatment of this disease (Tfelt-Hansen and Olesen, 1980). It is of interest that infusions of somatostatin, a peptide which inhibits the release of SP (Brodin *et al.*, 1981), reduced the pain of cluster headache in a recent double-blind study on 8 patients (Sicuteri *et al.*, 1984).

Experiments on axonal transport have suggested the existence of SP as well as other neurotransmitters in trigeminovascular fibres. When wheat germ agglutinin was applied to the middle cerebral artery using a polymeric delivery system (Moskowitz *et al.*, 1981*b*), both SP and wheat germ agglutinin were localized in small diameter ganglion cells (25–65 μm) (Liu-Chen *et al.*, 1984*b*). However, only 20 per cent of positive cells contained SP. Subsequently, cholecystokinin-like immunoreactivity was measured biochemically by RIA (Moskowitz *et al.*, 1983*c*) and found in perivascular fibres in whole mount preparations of feline, rat and guinea pig pial vessels. Excision of the feline trigeminal ganglion resulted in a significant decrease in the number of stained fibres on the ipsilateral side (Liu-Chen *et al.*, 1984*a*). Gastrin-releasing peptide, shown by others to be within primary sensory neurons (Panula *et al.*, 1983) and present around pial arteries (Uddman *et al.*, 1983), may also derive from trigeminal connections. Recently, enkephalin immunoreactivity was found in perivascular fibres (Moskowitz *et al.*, 1983*c*). The enkephalins inhibit SP release from primary sensory axons (Jessell and Iversen, 1977; Lembeck *et al.*, 1982) and thereby may be of significance for the physiology and pharmacology of trigeminovascular neurons.

Prior clinical and experimental evidence in man suggested that some perivascular fibres project from trigeminal and upper cervical nerves (*see* Moskowitz *et al.*, 1981*a*, 1984). Thus when large cerebral arteries, for example, were stimulated mechanically, subjects experienced painful sensations in the ipsilateral forehead in areas innervated by the first trigeminal division (Ray and Wolff, 1940). Infusions of histamine intravenously, known to cause bilateral frontal and occipital headaches (Pickering and Hess, 1933), failed to elicit pain in the deafferented hemicranium in humans who had undergone unilateral trigeminal rhizotomy (Clark *et al.*, 1936). The occipital headache was unaffected. By contrast, bifrontal headaches were present when histamine was given to subjects with lesions of the second and third trigeminal divisions, or lesions of peripheral branches of the trigeminal system, cranial nerve VII and IX, or the stellate ganglion. When surgical lesions were performed to treat severe intractable vascular headaches, a therapeutic effect was achieved only when the first trigeminal division was rendered analgesic (*see* White and Sweet, 1969). When pain and discomfort accompanied cerebral angiography, the sensation was referred to the ipsilateral forehead. The same distribution of pain referral was reported following thromboses or embolic strokes affecting the middle cerebral artery (Fisher, 1961). Moreover, frontal and occipital headache was observed following thrombosis of the basilar artery (Kubik and Adams, 1946). The occurrence of ipsilateral cerebral angiitis and contralateral hemiparesis subsequent to herpes zoster ophthalmicus also suggests the existence of trigeminovascular fibres in man (Gordon and Tucker, 1945; Hilt *et al.*, 1983). Proximal segments of the anterior, middle and posterior cerebral arteries show segmental narrowing (Gilbert, 1974; MacKenzie *et al.*, 1981), and fatal cases exhibit inflammatory changes as well as virions in the walls of involved vessels (Doyle *et al.*, 1983). It should be noted that headache in the above cited examples may in some instances arise from sensory axons other than those surrounding large cerebral arteries. The frontal location of headache, nevertheless, implies nociceptive transmission along trigeminal fibres and supports a possible relationship between this nerve and pain sensitive structures within the cranium, including the cerebral blood vessel.

The observations reported herein would fit the expected pattern of innervation if similar experiments were possible in man. For example: (1) pain in man was elicited by electrical or mechanical stimulation only from large blood vessels and not from adjacent pial tissues; levels of substance P were 20 to 30 times higher in vessels as compared with surrounding pial tissue; (2) pain was felt over the contralateral hemisphere when the superior sagittal sinus was stimulated electrically in man following unilateral trigeminal deafferentation; some midline structures receive a bilateral innervation; (3) pain due to some lesions in the posterior fossa are referred to the trigeminal receptive fields (Cushing, 1931). Indeed, frontal headaches were reported in 70 per cent of cerebellar tumours in one large series (Bailey *et al.*, 1939). Involvement of trigeminal fibres innervating the superior cerebellar artery would provide one possible explanation for the occurrence of frontal head pain in this situation. The apparent anatomical similarities described between the cat and man are remarkable, and especially so in view of some striking contrasts between their cerebral circulations. For example, the adult feline internal carotid artery is vestigial and the internal maxillary artery provides the major source of blood to the intracranial internal carotid artery *via* the *rete mirabile*.

An anatomical basis for referral of pain from cerebral arteries was investigated recently by studies in which different neuronal tracers were applied to the middle meningeal or middle cerebral arteries and the supraorbital nerve in monkeys and cats (Borges and Moskowitz, 1983; McMahon *et al.*, 1985). In these animals, no double labelled cells were found in the trigeminal ganglion as would be expected if the forehead and the vessels received dichotomizing axons from the same ganglion cells.

So far, there have been no reports showing a functional relationship between sensory perivascular fibres, related peptides and permeability changes in the CNS as there have been in the extracranial cephalic circulation (Bill *et al.*, 1979; Couture and Cuello, 1984). Systemic capsaicin or SP infusion failed to increase the extravasation of Evans blue-albumin complete in the brain as it did in other organs such as the trachea, nasal mucosa and conjunctiva (Saria *et al.*, 1983). Electrical stimulation of feline trigeminal ganglia caused ipsilateral miosis and leakage of vital dye into the anterior chamber of the eye, similar to observations in the rabbit (Bill *et al.*, 1979), but did not increase permeability of cerebral vessels (T. V. Norregaard and M. A. Moskowitz, unpublished observation). It is noteworthy that the axon flare (Bruce, 1913; Lewis and Grant, 1924) could not be elicited in the pial circulation by chemical or mechanical injury (Florey, 1925), although increases in cerebral blood flow reportedly followed trigeminal nerve stimulation in two reports (Lang and Zimmer, 1974; Lance *et al.*, 1983). SP relaxed canine (Couture *et al.*, 1980) and feline cerebral arteries (Edvinsson *et al.*, 1981) at threshold concentrations of 1 pM and 10 nM, respectively.

Regardless of whether sensory nerve fibres alter the permeability or calibre of cephalic arteries, pain from intracranial and extracranial arteries, both of which have been implicated in migraine, must be conveyed by the described pathways to the central nervous system. Hence a study of the anatomy, biochemistry and pharmacology of trigeminal connections, and attempts to modulate the activity of these nerve fibres, should prove worthwhile as the focus for strategies to reduce the frequency, intensity and duration of headaches.

ACKNOWLEDGEMENTS

These studies were supported by grant NS 10828-11 from the National Institutes of Neurological and Communicative Disorders and Stroke and a grant-in-aid from the American Heart Association. Dr Moskowitz is an Established Investigator of the American Heart Association. The tissues for studies reported in Table 1 were kindly provided by Dr John A. Bevan, University of Vermont, Burlington, VT. We thank Drs Lee-Yuan Liu-Chen, and Marc R. Mayberg for advice and gratefully acknowledge the technical assistance of Peter Barley and Robert Weatherwax. The assistance of Margaret E. Lally in the preparation of the typescript was appreciated.

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(*Received May 25, 1984. Revised November 7, 1984. Accepted December 31, 1984*)

Brain (1985) **108**, 535–536

MAGNETIC RESONANCE IMAGING (MRI, NMR) SCAN IN A CASE OF CALLOSAL APRAXIA AND PSEUDONEGLECT

by R. T. WATSON, K. M. HEILMAN *and* D. BOWERS

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We reported a patient with isolated apraxia of the left hand from a spontaneous callosal disconnection (Watson and Heilman 1983). This patient supported Liepmann's concept that the left hemisphere is dominant for action. She also showed pseudoneglect and this was reported in another study (Heilman *et al.*, 1984). Multiple CT scans demonstrated infarction of most of the body of the corpus callosum with sparing of the genu, the posterior one-fourth to one-fifth of the body and the splenium. There was no evidence of cortical damage by CT scan. We

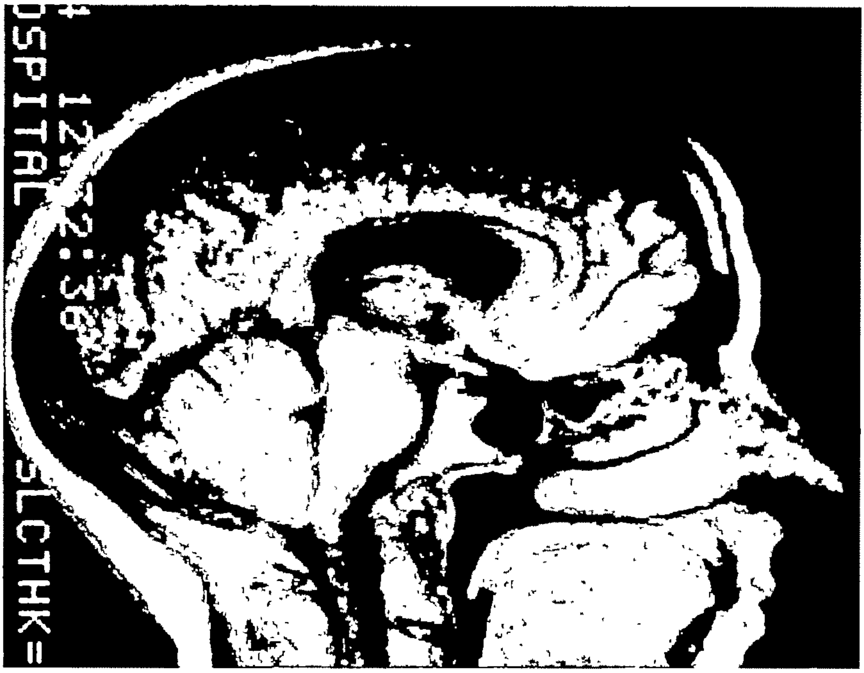

FIG. Sagittal MRI scan demonstrating infarction of most of the body of the corpus callosum.

recently obtained an MRI scan on this patient (*see* fig.) that confirms the CT localization more precisely.

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NOTICES OF RECENT PUBLICATIONS

Myasthenia Gravis. By Hans J. G. Oosterhuis. 1984. Pp. 261. Edinburgh: Churchill Livingstone. Price £25.00

With this scholarly monograph, Dr Oosterhuis comes of age as a myastheniologist, twenty-one years having now elapsed since his Ph.D. thesis on the clinical and pathophysiological features of this disease was published. The introductory historical review serves to emphasize that this period has seen remarkable advances in our understanding of this disorder, particularly in the last decade. Dr Oosherhuis' many publications over the period provide evidence of his continuing interest in the disease and of his own contributions to knowledge.

The reader quickly appreciates the breadth of the author's practical experience in the chapter on the clinical aspects of this disease. The clinical descriptions are particularly good, with useful discussions on methods of assessment, and on differential diagnosis (Chapter 7). Ocular myasthenia in particular may cause diagnostic difficulties, and to the differential diagnoses listed, the reviewer would add mitochondrial myopathy which in two recent personal cases has presented as unilateral ptosis.

In his review of areas where controversy exists, the author is almost too even-handed. On the question, for example, of whether the benefits claimed for thymectomy are justified or of which operative route (transsternal or transcervical) should be used, the evidence is presented somewhat uncritically, perhaps because of concern to avoid prejudice. This may leave the uninformed reader in some uncertainty about what conclusions he is supposed to draw. In the case of the operative approach, for instance, the reviewer would regard the evidence as strongly weighted in favour of the transsternal approach.

The description of the physiology of neuromuscular transmission does not specify the species to which the quoted values apply, and one might assume it to be man. But if so, the values given for quantal content are much too high and seem more likely to refer to mice than men. This chapter includes a description of the effects of acetylcholinesterases, muscle relaxants and other agents acting at the neuromuscular junction.

Congenital myasthenia could usefully have been distinguished more clearly from myasthenia gravis. It is included in a section on 'myasthenia gravis in infancy', and thus might give the casual reader the impression that this syndrome is a subgroup of myasthenia gravis, whereas in reality it is a nonimmunological, inherited heterogeneous group of disorders.

The value of antiacetylcholine receptor antibody measurement in diagnosis is stressed, and there are some good illustrations of the relationship between antibody titre and clinical state in longitudinal studies of individual patients. But the author is cautious about interpreting the role of the antibody in causing muscle weakness (Chapter 5) and, curiously, he does not mention in this context the evidence for its involvement in the complement mediated lysis that clearly occurs at the postsynaptic region in severely affected cases.

The section on treatment includes a full description of symptomatic (nonimmunological) treatments, which are becoming of less importance now with the increasing use of immunosuppressive drug treatment. The reader may find some difficulty as he proceeds through this chapter in discerning what in practice he should do faced with a myasthenic patient, and it is only when the summary at the end of the chapter is reached that practical guidelines are outlined.

The points raised above are minor criticisms only. This is an excellent book, with particular strengths in the clinical aspects of the disorder. The bibliography contains over a thousand entries (up to 1982), and each chapter concludes with a summary. The volume will provide a valuable source of information for all those with an interest in this disease.

J. Newsom-Davis

Neurologic Emergencies in Infancy and Childhood. By John M. Pellock and Edwin C. Myer. 1984. Pp. 418. Philadelphia and London: Harper and Row. Price £30.00.

This is a well produced, well illustrated and very readable book, with its independent contributions covering a wide range of topics including seizures, trauma, coma, poisoning, stroke, ataxia and infections, and neuromuscular, neuro-ophthalmological and endocrine aspects, and spanned by sudden infant death at the beginning and brain death at the end. There is an epilogue of three additional contributions on the value of neuroradiology, electroencephalography and electromyography in emergencies.

It may seem a bit strange to devote the first chapter of a book on neurological emergencies to near-miss sudden infant death syndrome, but this enigmatic multifactorial problem has in recent years captured the interest (or perhaps imagination) of almost every subspecialty in paediatrics, ranging from respiratory physicians through cardiologists to infectious disease experts and recently even Home Office pathologists. Apnoea and control of breathing are certainly within the remit of the nervous system.

I had anticipated that a book under this title would concentrate on the practical aspects of diagnosis and acute management of the various emergency problems and was disappointed that the approach was much more of an academic one concentrating on the pathophysiology and background information on the disorders, with the therapeutic side often lost in the midst. There is also a tendency in the interests of being complete and exhaustive to provide long lists of unlikely causes to be eliminated rather than starting off with and concentrating on the most important, most likely or therapeutically most reversible ones. Thus the section on acute weakness in children is subdivided anatomically and the subsection on neuromuscular junction lists botulism (fair enough in the United States), hypermagnesaemia, Eaton-Lambert syndrome (in children?), black-widow spider venom and shellfish poisoning before myasthenia, and in the section on myasthenia makes no mention at all of the common presentation of the childhood form of myasthenia as a choking or apnoeic spell or a possible seizure, which may be fatal unless the diagnosis is suspected.

There are a number of exceptions, such as the chapter on status epilepticus, the one on neuro-ophthalmology (which has a useful algorithm of visual loss), and the one on poisoning which is very methodical and practical and covers the clinical effects and management for a wide range of drugs and chemicals as well as approaching the problem from the point of view of presenting features such as convulsions, agitation, ataxia, weakness, etc., and finally providing a concise review, with treatment, of various bites and envenomations.

There is a vast amount of interesting and useful information in this book and I would consider it an excellent publication under the wrong title—it more appropriately is a treatise on acute neurological problems in infancy and childhood. If it was intended, as the preface suggests, for 'emergency physicians, pediatric neurologists, pediatricians . . . all of whom must make immediate decisions when they are confronted with neurologic emergencies in infants and children,' it would have benefited from a different emphasis or else needs a highlighting pen to extricate the relevant bits from the background reading.

This book should provide a valuable reference for neurologists or paediatricians interested in the neurology of infancy and childhood.

V. Dubowitz

Neural Mechanisms of Pain. Advances in Pain Research and Therapy, Volume 6. Edited by Lawrence Kruger and John C. Liebeskind. 1983. Pp. 364. New York: Raven Press. Price $61.00.

This volume is one of a series sponsored by the International Association for the Study of Pain, the stated aim being to review areas of current research into neural mechanisms of pain. There are 21 contributions from over 40 authors, who are recognized authorities in their fields. In the opening chapter, Bonica puts the present interest in all aspects of chronic pain in historical perspective, and succinctly summarizes areas of important recent advance. The authors of the ensuing chapters have each introduced their contributions with a brief review of work leading up to the current research discussed. These surveys are almost all well written, and on this basis alone the book should appeal to a wide audience.

The order of the chapters is conventional, starting at the periphery, moving to the spinal cord and then rostrally. This is a pity, since two excellent cautionary chapters, by Melzack, on measurement of pain, and by Price, on the relationship of psychophysical analysis to neurophysiology, are found at the end of the book, when they should appear at the start. Melzack continues his crusade for a wider approach to the problem of chronic pain, offering no simple definitions, and outlining the fallacies of adopting a telephone cable view of pain mechanisms. The development of a means of describing pains of various kinds in terms of sensory and affective qualities and evaluative description is briefly but clearly set out, showing the way in which the McGill Pain Questionnaire has evolved. Scoring the questionnaire to document changes in a patient's pain is discussed, together with its potential diagnostic value and its usefulness in distinguishing organic and psychogenic pain in some instances. For clinicians, this chapter contains obvious truths, but one hopes that experimental animal neurophysiologists will take the trouble to read it and heed its message.

Returning to the earlier chapters, Perl reviews peripheral nociceptors and their terminations in the dorsal horn. Ochoa traces the development of single afferent C fibre recording by microneurography in man. Much has been learnt in normal nerves, but its value in the investigation of patients with pain with nerve injury remains to be assessed. LaMotte discusses the behaviour of cutaneous nociceptors in normal and hyperalgesic skin in experiments in man and monkey, showing that the hyperalgesia outlasts the discharge of the nociceptors, indicating a central basis in part for the hyperalgesia. Iggo *et al.* describe the reduced threshold responses of A delta and C fibres in the Freund's adjuvant-induced arthritis in the rat. This looks like becoming an important model of chronic arthritis, offering particularly an opportunity to examine chronic spinal cord changes.

In a typically wide-ranging account, Wall summarizes mechanisms of acute and chronic pain in peripheral nerve and spinal cord. The exciting recent development here is the recognition of spinal cord changes in chronic injury, with chemical and physiological changes taking place over days, implying circuitry modifications in the dorsal horn. Wall has introduced the concept of connectivity control to embrace these changes; the factors governing the changes are of crucial importance to an understanding of chronic pain.

The peptides in the dorsal horn and their possible functions are discussed by Dodd *et al.* At best, the evidence suggests a slow transmitter role for substance P, with less good reasons in support of a transmitter function for the seven or so other peptides identified in the dorsal horn. Some interesting data suggesting that ATP may be a transmitter in the dorsal horn are also discussed. This is followed by a discussion of the evidence in favour of involvement of 5HT in the descending pathway from the medulla mediating stimulation-produced analgesia and morphine analgesia, by Rivot *et al.* Dubner and colleagues present elegant immunocytochemical and HRP data on the interrelationships between descending 5HT and local enkephalin input and intrinsic dorsal horn circuitry, finding that dorsal horn projection systems receive dual, pharmacologically distinct, descending and segmental inhibitory inputs. A broad view of the possible relevance of these findings to mechanisms other than analgesia is taken; such systems may permit suppression of irrelevant afferent activity, allowing extraction of behaviourally important information from the environment.

Albe-Fessard *et al.* discuss the interesting clinical observation that in patients with deafferentation pain, stimulation in the medial thalamus causes pain or reproduces their pain, but does not in patients with movement disorders, suggesting that some type of facilitation develops in the pain patients. In an experimental study, they show that in the presence of deafferentation, the cortex exerts a facilitation on the medial thalamus, to which the spinothalamic tract projects, providing a possible substrate for this effect. Ralston reviews the anatomy of the spinothalamic tract and cortical projections.

Yaksh examines the increasingly complex spinal opiate receptor mechanisms involved in analgesia, where μ and δ receptors seem to be most important. Willis reviews the many influences on dorsal horn nociceptive neurons. Particularly interesting is the finding that cortical or brainstem stimulation may produce inhibition or excitation of spinothalamic tract cells. A cautious view is correctly expressed concerning an exclusively analgesic role for such dorsal horn cells. Fields discusses the confusing physiological and pharmacological data concerning brainstem analgesia mechanisms, while Mayer and Watkins examine the broader issues of multiple opiate and nonopiate analgesia systems, embracing the possible mechanisms of transcutaneous electrical stimulation and acupuncture-induced analgesia. Lewis *et al.* address the important problem of identifying the types of natural stimuli which activate endogenous analgesic mechanisms, and which of these are opiate and which are nonopiate-mediated. In their studies, a short noxious stimulus seems to activate a nonopiate system, whereas a more prolonged (20 min) stimulus activates an opiate pathway. This is interesting work, but the relevance of such experiments on acute pain to chronic pain in man is open to question.

Young *et al.* provide an excellent, well-balanced view of the current confusing situation regarding deep brain stimulation for chronic pain in man, presenting their own results in 33 patients and reviewing reports of 694 patients in the literature. In their hands, patients with pains of peripheral origin did much better than those with deafferentation pains. Periventricular grey stimulation was as effective as periaqueductal grey stimulation, and the former much preferred by patients; thalamic stimulation gave poor results. No consistent changes were found in beta-endorphin levels with stimulation in this series. Despite a complication rate of 21 per cent, the results were judged good in this carefully selected group of patients. The discussion in this chapter is particularly informative. A chapter by Vierck and Cooper on the problems of using simple behavioural assays in animals as measures of analgesia should be read by all laboratory workers.

Overall, this is an extremely useful volume, both for neurophysiologists and clinicians with an interest in the treatment of chronic pain. It is rare for books from symposia to be so comprehensive and to achieve such coherence as a whole. It is relatively inexpensive, and can be highly recommended both to those with an established interest in pain and as an introduction to those coming fresh to the subject.

J. W. SCADDING

Cluster Headache. Edited by Ninan T. Mathew. 1984. Pp. 156. Lancaster: MTP Press. Price £23.50.

Migrainous neuralgia or cluster headache must rank highly in the stakes for neurologists' favourite disease. It is strange that it is still seldom diagnosed at presentation, thus affording the opportunity to score over ones colleagues; treatment too, has been less than satisfactory in many instances. Why this should be so is a mystery, the clinical features being so distinctive, so well and succinctly described in texts of medicine and neurology and, generally gratifyingly responsive to appropriate treatment.

Perhaps because there is little known about its pathogenesis, books, even those devoted to headache or migraine, are aptly modest in the length of their descriptions. And yet the syndrome is of considerable importance, posing fundamental questions about the cause of headache which remain unanswered. Is it a variant of migraine, or are the curious preference for men, its more strict unilaterality, the almost constant autonomic signs in each attack, and above all its curious rhythms of clusters and nightly assaults closely related to REM sleep—all features which demarcate it as a separate neurovascular syndrome?

The American Association for the Study of Headache confronts these problems with the first of a planned series of 'advanced courses' on the topic of Cluster Headache. Fourteen chapters and 135 pages, mostly unillustrated will cost the private buyer £23.50. The contributors are mainly those experts from specialized headache clinics rather than their British counterpart, the clinical neurologist with an interest in headaches.

Kunkle's description of the acute syndrome is characteristically excellent. He then proposes a classification into acute and chronic types and an uncomfortably based group of four variants. Cluster migraine, cluster-tic and cluster-vertigo will not gain universal acceptance in this context; the nosology of chronic paroxysmal hemicrania is equally uncertain. There are good sections on the history of the disorder (William Speed), variants (Diamond) and a sound review of the pathophysiology (Edmeads). Much of the remainder is rather pedestrian, repetitious, and abounds with spelling errors and grammatical solecisms which should not have escaped the editorial eye. Claims for personality types (the affected male—Leo the lion pulled along in a red wagon by his wife the powerful mouse) are fanciful; and the stress laid on psychological factors is not fully supported by scientifically acceptable data. A more detailed account of more fundamental knowledge and an exposure of our many areas of ignorance is lacking. Only brief allusion is made to existing papers on blood flow studies, thermography and angiography. And the possible importance of histamine, prostaglandins, serotonins and male hormones, though well summarized by Edmeads, merits more detailed consideration, and additional chapters.

The chapters on treatment of both acute (Couch) and chronic (Mathew) types are well covered with useful summaries of available drug trials and with much to say about lithium toxicity and monitoring (though this is not a major problem in practice). Dalessio reviews with apt brevity the surgical approaches to the sphenopalatine ganglion and trigeminal root, and a series of four case reports about resistant cases ends the book, reminding us of the frustrations we all experience at some time with these patients.

The only other books I know which are devoted to this enigmatic disorder are Wilfred Harris's seminal description of *The Facial Neuralgias* (1937) and Kudrow's monograph (OUP, 1980). Of the two recent works, I prefer Kudrow's as a more detailed and factual record of recent clinical data and investigation.

J. M. S. PEARCE

Functions of the Basal Ganglia. Ciba Foundation Symposium 107. 1984. Pp. 281. London: Pitman. Price £26.50.

A limited degree of cross-talk has been occurring for some time in the basal ganglia world. The CIBA think-tank, which took place in November 1983, consolidated this trend by bringing together an equipe of distinguished neurobiologists in the hope that the muse of 41 Portland Place would free some of them from the shackles of their own paradigms. Their brief was an exciting one: the geography of the basal ganglia is changing quickly, the pioneer chemical maps are now fusing with traditional circuitry and Golgi staining and horseradish peroxidase techniques have revealed a bewildering complexity of neuronal cell types even within the 'liver of the brain', the corpus striatum. Graybiel's striosomal mosaic raises the possibility that new connections could occur during life based on changing experience and emphasizes the immense potential of the corpus striatum for functional heterogeneity. Thought may be considered as movement not connected to a motor neuron, and the copious dialogue between the basal ganglia and the limbic system provides ample anatomical ammunition to explain the exquisite influence of mood and motivation on motor function. The ventral striatum has its own circuits and probably its own modulating roles connected more with 'cognition' than movement. In this regard it is intriguing that this structure appears to be relatively spared in Huntington's disease. Single cell recording techniques and increasingly sophisticated psychological perceptuomotor tests seem to suggest that the role of the basal ganglia with respect to motor control may be to activate previously prepared movements and to select and sequence motor programs to form motor plans. The corticostriate fan results in the organization of cortical areas in series with their principal neostriatal regions, thereby enabling functional regional striatal specialization. Most of the motor fibres from the striopallidal complex, after relays in the thalamus, terminate in the supplementary motor cortex and it is of interest that lesions at this site often closely resemble those negative symptoms found in Parkinson's disease.

The clandestine *in camera* format of these meetings always engenders paranoia in those who are involved in the field but excluded; the subsequent publication is awaited with a mixture of irritation and curiosity and the incubation period can be tormenting if too long. Why should this be? The papers themselves are predictable, the party line of the speakers well known and the ideas can all be found elsewhere in original publications. Quite simply it is the printed discussion, demoniacal ideas for new studies appearing on almost every line and enabling those present to steal a march on the rest of us. Oracle number 107 is a perfect statement of a very imperfect art; many of the lines of scientific research seem sealed off and riddles abound. Nevertheless, if one is to crack the enigma of these buried hives which link mind and movement further offerings of this sort should be welcomed and encouraged.

A. J. LEES

Cerebral Ischemia. Edited by André Bes, Pierre Braquet, Rodolfo Paoletti and Bo K. Siesjö. International Congress Series 654. 1984. Pp. 396. Amsterdam: Excerpta Medica. Price Dfl. 205.00.

This is not a cohesive textbook on cerebral ischaemia but the proceedings of the third international symposium on the cerebral circulation held in Toulouse in 1983. The two main themes of the conference were first, neuronal vulnerability and secondly, free radicals and icosanoids.

The reader should not be put off by the Preface, which attempts to massacre the English language. There are some excellent chapters, beautifully written, but there is a marked lack of uniformity. Some are short reviews of important topics, others are long accounts of the authors' own work in narrower areas.

The justifications for publishing 'proceedings' are that those who attended are provided with a record of the conference and those who missed it can discover what was said. Proceedings therefore need to be published quickly and preferably cheaply. This is an expensive hardback produced by a photographic process, which should have allowed more speedy publication. With such delay, much of the valuable original material presented in such collections will have been published elsewhere.

D. J. THOMAS

Peripheral Neuropathy. Second edition. Two volumes. Edited by P. J. Dyck, P. K. Thomas, E. H. Lambert and R. Bunge. 1984. Pp. 2333. Philadelphia: W. B. Saunders. Price £130.00.

This huge book, familiar from its first edition in 1975, represents the fruit of the efforts of a large number of clinical investigators and laboratories in various countries. Our improved understanding of the pathogenesis and pathology of peripheral nerve disease has resulted, in large part, from advances in histological, biochemical, immunological and physiological techniques for studying peripheral nerve disease, and from the intensive study of certain naturally occurring peripheral neuropathies in species other than man. This new knowledge is reflected in greater awareness and understanding of the clinical phenomenology of peripheral nerve disease and, perhaps to a lesser extent, in improvement in management and treatment of these disorders.

Early attempts to understand peripheral nerve diseases were hampered by the lack of appropriate methodology and the most painstaking histological and physiological investigations were required to breathe an understanding into these problems. In this book the authors, now expanded to four with the addition of Richard Bunge to the original trio, have persuaded 145 colleagues from many different countries to describe and review the peripheral neuropathies, and other studies in neurobiology relevant to understanding this group of disorders. The two volumes can be used separately. Clinical aspects of peripheral nerve disease are considered in Volume 2 in a logical and didactic classification that some might consider extends beyond any reasonably strict definition of peripheral neuropathy. For example, motor neuron disease and the spinal muscular atrophies are reviewed in considerable detail under the heading 'Inherited peripheral neuropathy'. This somewhat curious juxtaposition has come about because the authors have stressed the relationship between primary pathological processes occurring in the cell bodies of the peripheral nerves, that is the anterior horn cells, posterior root ganglion cells, and autonomic ganglia, to diseases of the axons and other peripheral nerve structures in their concept of these disorders. Volume 2 will probably be much more greatly used than Volume 1, since the latter is mainly concerned with studies related to the basic science of the peripheral nervous system and it is thus by Volume 2 that this expensive book will stand or fall for the clinician. Each chapter in this volume is self-contained, providing a comprehensive account of its subject. References follow each chapter, a practice that leads to much duplication and that is somewhat inconvenient for the busy reader looking something up in the book. Since the book is the product of the work of many different authors there are inevitable differences in style between the various chapters. As one would expect, the Mayo Clinic contributions are veritably encyclopaedic, even when, as in the case of certain of the inherited sensory neuropathies, there are only one or two cases recorded. Nonetheless, there are very few areas in which the reader can conclude that a less than full account of a problem has been given. A rather brief and unsatisfactory discussion of peripheral neuropathy in the acquired amyloidoses is perhaps one example of an incompletely thought out description. In virtually all chapters a rigorous account of biochemical and other basic science aspects of the pathology and physiology of the neuropathies is given and this forms an invaluable source of reference, often in areas quite distinct from peripheral neuropathy itself. Volume 2 is thus of immediate and practical value to all clinicians.

Volume 1, on the other hand, is inherently less satisfactory. It consists of seven sections following an introduction by Buchthal. These sections relate to structure and function, development and regeneration, molecular biology, functional compartments (vascular permeability and endoneurial pressure), pathology, nerve conduction and EMG, and quantitative evaluation of the clinical deficits. Clearly, these headings indicate that one is confronted by a textbook of neuroscience, related to medicine. It must be asked whether this effort was worthwhile and the answer to this question must stand or fall on whether the reviews contained in the 1100 pages in Volume 1 possess information that is not readily available elsewhere. It has to be said at once that in many cases this is not so. For example, nerve conduction, EMG, single fibre EMG, microelectrode recordings from human nerves, and compound action potential studies in sural nerve biopsies, are topics that are described in greater detail in a large number of standard textbooks, conference reviews, annual reviews and journals. Cerebral evoked potential studies fall into the same category. Indeed, many of these chapters simply reiterate material already published by the same authors elsewhere and, in some cases, the descriptions available in this book have definitely lost their freshness. Similar criticisms apply to descriptions in relation to other topics. The anatomy of the peripheral nervous system has been constantly the subject of review for many years and it cannot really be said that the reviews of this subject in this volume represent an improvement on those available elsewhere. The muscle spindle is described in Chapter 7 by Professor Boyd, arguably one of the leading authorities on this subject, but the description given relates almost entirely to studies of the physiology and anatomy of muscle spindles in the cat. The relevant aspect of this chapter, as in so many of these basic science chapters, is contained in the last three columns (1½ pages) in which the studies of the pathology and physiology of muscle spindles in man are rather briefly described, although without any attempt to relate these to the preceding discussion of cat physiology and anatomy. The Golgi tendon organ receives only a few pages, again largely concerned with studies in species other than human. The peripheral sensory system suffers from lack of space. This is clearly a very large subject and only superficial aspects of it can be touched on in a single chapter. Because of the direction of the book towards encyclopaedic reviews, the authors of reviews intended to deal with very large subjects such as this have not been enabled to direct themselves to any particular aspects and, as a result, there is too much information within a short format, and yet the information given is intrinsically unsatisfactory because incomplete and, often, not fully considered. Other aspects of the list of contents of Volume 1 illustrate the extraordinary diversity that the editors have allowed to creep into the volume. For example, the autonomic innervation of the gut, the bladder, the blood vessels, the eye and the heart receive separate chapters and, again, one cannot help remembering that each of these subjects has recently been the subject of monographs extending to 400 pages or more.

In short, this book represents the result of a tremendous and scholarly attempt to provide an encyclopaedic review of peripheral nerve disease for everyman. For the clinician Volume 2 is an excellent, dependable and thorough account of clinical and relevant investigational aspects of knowledge of these disorders, if a little repetitious in some chapters and perhaps lacking in restraint, particularly in relation to the amount of space devoted to some of the more extremely rare disorders described. Volume 1 is less satisfactory, and represents an attempt at the impossible. The material contained in the reviews in this volume is available in more useful format elsewhere. I wonder if my bookseller will let me have Volume 2 on its own?

MICHAEL SWASH

Oncology of the Nervous System. Edited by Michael D. Walker. 1983. Pp. 413. The Hague: Martinus Nijhoff. Price Dfl. 160.00.

This volume is one in a rapidly expanding series published during the past four years of reviews in specific areas of cancer research and treatment. Neuro-oncology is now a fast moving field and this book contains 15 chapters by 27 distinguished contributors on assorted topics. All but one of the chapters concern malignant brain tumours, either primary or secondary, the exception being devoted to functioning pituitary tumours. It is not a comprehensive review of the field, for example diagnostic neuropathology is omitted. However, it does cover not only the important areas of surgery, radiotherapy and chemotherapy, but also some frequently neglected areas including epidemiology, clinical prognostic factors, biological effects of corticosteroids and metabolic therapy by amino acid deprivation. This book is well printed and the illustrations well reproduced. It can be recommended to specialists in the field and it should be available in any department of neurology or neurosurgery concerned with recent progress in neuro-oncology.

D. G. T. THOMAS

Progress in Experimental Tumor Research. Volume 27. **Brain Tumor Biology.** Volume 28. **Brain Tumor Therapy.** Edited by M. L. Rosenblum and C. B. Wilson. 1984. Pp. 258 and 288. Basel: Karger. Price DM 282.00 and DM 188.00.

These two most recent companion volumes in a series devoted to progress in experimental tumour research address the fields of basic biology and clinical treatment of brain tumours. There are 28 chapters produced by a large international group of authors. The principal topics in the first volume are carcinogenesis, new approaches to neuropathology of brain tumours, including chromosomal analysis and immunohistochemistry, tumour metabolism and physiology and cellular resistance to treatment. The second volume considers recent new approaches to cytotoxic therapy, immunotherapy, and novel applications of radiation including interstitial radiotherapy, as well as hyperthermia and ultrasound. It is an indication of the activity and progress in this field that a supplementary reference list to additional recent developments in this field including oncogene expression, growth and angiogenesis factors, predictive tests of tumour responsiveness, and new forms of therapy by surgery, radiation and cytotoxic agents has been provided as an appendix. The two volumes provide a comprehensive review of current concepts and innovative ideas in the field. The books are well produced on good paper and well illustrated. They will be of interest to specialists in the field as well as to others in the neurosciences who wish to have a summary of current trends in brain tumour research.

D. G. T. THOMAS

Human Developmental Neuropsychology. By Otfried Spreen, David Tupper, Anthony Risser, Holly Tuokko and Dorothy Edgell. 1984. Pp. 474. Oxford University Press. Price £40.00.

So successful has been the collaboration between neurologists and neuropsychologists working with adults that one has become accustomed to a high level of discussion of refined theoretical issues concerning psychological function. The state of affairs in developmental neuropsychology is not of this kind and this book is perhaps necessarily much more empirical. In three of its four parts it is largely confined to presenting facts either concerning normal neural development (Part I) or its pathology (Part III), rather than with questions of plasticity, laterality or dominance. Similarly, there is little extensive discussion of dysphasia, dyslexia or the agnosias until Part IV, the last quarter of the book.

The text arose from a course and presumably is intended as a teaching text. It is rich in information, covers a wide range of topics and provides a good neurological, paediatric and pathological background for the neuropsychologist reader. For example myelination of different areas is discussed throughout Part I together with growth spurts and the development of association areas. Disorders associated with development are listed and discussed in Part III. Following the presentation of the AAMD classificatory system for childhood disorders in a summary form and the presentation of data concerning the frequency of neonatal deaths and infant mortality, separate chapters discuss sex-linked genetic disorders and chromosomal abnormalities, and structural abnormalities including anencephaly, hydrocephaly and spina bifida. An interesting suggestion is made, *inter alia* for a link between meningomyelocele and the phenomenon of superficial speech (p. 144). A full discussion of the educational consequences of low birth weight suggests that associated disorders are the most relevant sources of learning defects, hypoxia, intracranial haemorrhage, toxaemia and neonatal asphyxia, for example. Further chapters in Part III discuss the effects of syphilis, toxoplasmosis, rubella, cytomegalovirus, marasmus and kwashiorkor with their consequences of lowered IQ and poor attention span. Reading between the lines one might wonder where exactly the boundaries between neuropsychology and the psychology of subnormality or clinical psychology might ultimately be drawn.

However, just at this point with Chapter 17 on hemispherectomy and the subsequent Part IV one begins to read more of what might reasonably be regarded as the proper preserve of developmental neuropsychology. The history of the concept of minimal brain damage is once more discussed with the usual conclusions (Chapter 18), and attentional disorders mentioned. A number of neuropsychological issues such as plasticity, functional crowding and theories of dyslexia are broached but given short shrift until Chapter 23, very close to the end of the book. Here at last the age at which the hemispheres perhaps cease to have equal language potential, capacity to recover from damage and the causes of deafness and dysphasia are more fully treated. A good summary table is offered on p. 315. The next chapter, however, on the subnormality literature is somewhat less successful, repeating a number of time-worn conclusions which are attributed to the authors' contemporaries. The last cognitive chapter on learning difficulties begins to tackle neuropsychological problems like dyslexia more theoretically; however, even here structure-function connections are left uncertain if not vague.

Where the material in this book is weak, therefore, is not in the good background which it undoubtedly provides, but in advancing any precise ideas about either structure-function connections, or any extensive discussion of important issues such as plasticity, dominance or specialization. The method section (Part II) is of variable quality. Chapters in this book are not signed and if the book is meant as a text for students it could be too expensive for them. Nonetheless, weaknesses aside, it is a very useful addition to a virtually nonexistent literature.

NEIL O'CONNOR

Sleep Mechanisms. Edited by A. Borbély and J. L. Valatx. 1984. Pp. 305. Berlin: Springer-Verlag. Price DM 70.40.

Physiologie du Sommeil. Edited by O. Benoit. 1984. Pp. 192. Paris: Masson. Price Ff. 198.00.

Thanks to the European Science Foundation, a winter school was held among the high mountains of Switzerland for a week in January 1983: the lectures given are published in the first of these two books. They are a tribute to the continuing vigour of European basic research (no American authors) and they are all in English, even though it is not the native tongue of any of the writers.

D. Elmqvist summarizes the changes in cerebral circulation of man and monkey that accompany sleep: a fall of blood flow in slow-wave sleep and a rise in REM sleep, though he does not mention the modern evidence that in REM sleep there is a loss of correlation between oxidative metabolism and blood flow in the brain. I enjoyed Irene Tobler's account of the phylogeny of sleep. We need sleep and if we have been deprived of it then we sleep more deeply: her cockroach too has its 24 h rest-activity cycle, it too is unresponsive in the rest phase, and if it has been deprived of rest, then it too rests more profoundly.

At sleep meetings one of the most impressive of speakers is L. M. Mukhametov from the USSR and in his chapter he not only tells us about the sleep of dolphins but also of seals. The dolphins remain the star attraction among aquatic mammals because they keep swimming and periodically breathing while asleep and they sleep with first one side of the brain and then the other. If one hemisphere alone is sleep-deprived then, he states, it is only that hemisphere that later catches up. But how on earth did he sleep-deprive one hemisphere at a time? There is much more to read, from the review of putative sleep substances, to the role of vagal afferents in sleep. Plenty to offer, plenty to disagree with, and worth buying.

Physiologie du Sommeil covers much the same ground with the help of 12 authors, all French. The style is slightly more of a didactic review. J. Foret gives a crisp account of normal human sleep in EEG terms, of the effects of sleep-deprivation, of the differences between morning and evening sleep, and of the variation in usual duration of sleep within the population: but he does not mention that these variations correlate with subsequent mortality rates. Odile Benoit discusses the human circadian rhythm of sleep and wakefulness in a more useful chapter than does the author in the rival book. Other writers dwell on cardiovascular and respiratory physiology in sleep and the investigation of sleep disorders. Overall, of the two books, the French one offers more for the clinician.

IAN OSWALD

Neurophysiological Approaches to Higher Brain Functions. By Edward V. Evarts, Yoshikazu Shinoda and Steven P. Wise. 1984. Pp. 198. Chichester and New York: John Wiley. Price £40.90.

The Neuroscience Institute was recently established to promote the study of scientific problems within the broad range of disciplines encompassed by neuroscience. Facilities are made available for visiting scientists to review specific fields of enquiry by extended discussion of theoretical and experimental work and to pinpoint future strategies for research directed towards a better understanding of higher brain function. The central theme under consideration by Evarts, Shinoda and Wise is the problem of 'preparatory set', which refers to the capacity of an animal to organize its impending motor behaviour. This book comprises the authors' survey of past work relevant to the neurons and their circuits whose activities may determine 'preparatory set', coupled with the outcome of discussions held at two conferences sponsored by the Neurosciences Institute, entitled 'Dynamic Cerebral Circuits' and 'Behavioural Correlates of Identified Cell Types'; these were attended by leading experts in fields ranging from neuroanatomy to neurophysiology and computer modelling of behaviour.

It has long been recognized from human experiments that an identical stimulus can trigger different behaviours according to the subject's intent. Indeed, intent itself, together with other attributes such as 'intended speed of response' or the 'degree of readiness' may be regarded as stimuli (generated by mentation) which govern the organism's response to external stimuli, although it is questionable for how long such states (usually imposed by the experimenter) actually carry the status of stimuli. The authors define 'preparatory set', as 'a state of readiness to receive a stimulus that has not yet arrived or a state of readiness to make a movement'. Following Hebb, this dual definition recognizes that selective attention in perceptual tasks is relevant to the understanding of 'motor set', while observations relevant to 'motor set' (e.g. reaction time, range or speed of movement, etc.) are often an essential component of studies of selective attention. Introductory chapters deal historically with this concept of 'set', but the ones concerned with set-dependent changes of movement, reflexes and volitional behaviour, although of interest in their own right, regretfully neglect important contributions by non-American workers to the debate concerning segmental *versus* suprasegmental levels of signal processing, especially as they relate to that grey area of what distinguishes reflex from voluntary movement in awake man. Notably, this neglect also extends to research by Scandinavian workers on the suprasegmental control of reflex and afferent transmission, which latter surely has to be considered as a mechanism that could be involved in 'perceptual set' and the process of selective attention. Although the authors emphasize that 'There is no sense in which the present volume is meant to be a thorough review' such statements never entirely protect authors from some reproach!

The middle chapters discuss the neuron types and information-processing capabilities of the cortex and the patterns of neuronal activity that possibly subserve the set-dependent behaviour. These data are discussed against an account of the relevant neural pathways in a chapter which is particularly valuable for the elegant synthesis it provides of the complex anatomical and functional interrelationships between cerebellum, thalamus and sensorimotor cortex and of the cortico-cortical connections between different functional zones of representation, be these coupled by direct pathways or *via* the deeper structures of the thalamus and pallidum. The penultimate chapter, which discusses the apparent advantages and disadvantages of different electrophysiological approaches, seems slightly misplaced, since its judgement on these fails in my mind to distinguish clearly between the kinds of information provided by different techniques and their relevance to the different questions posed by minds whose interests and objectives differ.

In summary, this is an important and interesting book defining the stance adopted by a distinguished group of authors in their approach to the neurophysiological study of higher nervous function. However, this stance is vaguely disconcerting since by adopting the policy that 'We intend largely to ignore the mechanisms of movement execution' the authors decouple the brain from the very apparatus through which we learn about its activity, namely motor behaviour. This policy leaves me uncertain as to whom the book is directed since too much is implicit for it to be entirely satisfactory for the naïve, while experts may not come comfortably to terms with its omissions.

Nevertheless the book is certainly a must for libraries serving neuroscience, although its price in the UK will undoubtedly deter the private buyer.

T. A. SEARS

Electrophysiology of Epilepsy. Edited by P. A. Schwartzkroin and H. V. Wheal. 1984. Pp. 420. Orlando, Florida: Academic Press. Price £42.00, $69.00.

This very interesting book is a collection of minireviews on the experimental approach to the study of epilepsy in animal models. Each author sets out to present his model with an approach which can be described as 'warts and all'. The models discussed range from the standard ones of the photosensitive baboon, alumina cream implantation, and topical and systemic penicillin application to the newer ones of iron salt application, the kindling of epileptic-like activity by electrical stimulation of the amygdala *via* indwelling electrodes, the aberrant responses of hippocampus after selective destruction with kainic acid and the use of a genetic strain of mouse with inherent epileptic-like activity.

A large number of chapters are devoted to the investigation of the responses of cells which give a large depolarizing shift in membrane potential which has superimposed upon it a high frequency burst of impulse activity, a characteristic of cellular discharge in the motor cortex in epileptic animals and *in vitro* preparations from mammalian neocortical or hippocampal slices or cultures of spinal neurons after various pharmacological insults and the normal behaviour of invertebrate nerve cells. Each author has the rather annoying trait of describing his particular model as being the best when each has such obvious failings and the differing techniques are at the present complimentary rather than exclusive. To give them their due, these failings are clearly stated by the authors and only one chapter is used as a semi-eulogy. One very interesting chapter poses the question of the role of the cells which make up the bulk of the brain, the neuroglia, on the production of epilepsy on their ability or inability to regulate adequately the ionic composition of cerebral extracellular fluid.

On the whole the chapters are clearly written, except that on the computer-modelling of aberrant hippocampal cell discharge which gets a little hazy at times. The chapters do not provide answers as to the basic mechanism of epilepsy but give a series of possibilities which require further exploration and pose many questions, not the least of which is why the high frequency discharge of cells in the motor cortex is only seen in the epileptic animal whereas such discharge is the norm in the adjacent sensory cortex. They do provide an easy compact guide to the state of the art plus a compact, if somewhat biased, review of the pertinent literature and, as such, would be a welcome addition to the reading list of anybody interested in the analysis of the epileptic state.

As a postscript one cannot help speculating on the numerical disparity this book poses. Is there really only one-sixth of the most important research on epilepsy going on outside North America?

A. ANGEL

Computer Aided Electromyography. Edited by J. E. Desmedt. **Progress in Clinical Neurophysiology,** Volume 10. 1983. Pp. 333. Basal: Karger. No price stated.

Professor Desmedt has invited 13 chapters from the main laboratories developing computer aided methods of EMG analysis. The book is a useful summary of present techniques and their applications. It is aimed at the clinical neurophysiologist rather than at the occasional user and it is a useful addition to the literature.

This collection of material emphasizes the most serious problems in the development and applications of computer aided procedures in everyday EMG examinations. They are those of the transportability of the computer programs used and control values from the originating laboratory to other laboratories. Much of the computing is done on particular configurations of particular types of machine, often expensive ones. For example, De Luca's deconvolution of individual motor unit potentials from patterns on voluntary effort requires hours of computer time and hours of careful work by trained operators.

Much of the work described in this book will require more development to put the techniques into the hands of ordinary users.

R. G. WILLISON

Otoneurology. Edited by W. J. Oosterveld. 1984. Pp. 274. Chichester: John Wiley. Price £27.00.

According to the editor this publication is intended for both the clinician and research worker who wish to familiarize themselves with noninvasive methods of otoneurological investigation, especially concerning the ocular motor system. As in any multiauthor book there are parts that are good. Thus the review of vestibular neurophysiology by Parker is a reasonable introduction to the subject with many key references up to 1980, and Honrubia and Luxon's chapter details well the former's view of optokinetic nystagmus. The inclusion of chapters on auditory function is obviously valuable in any book on otoneurology since it is so often affected at the same time as vestibular function. Hinchcliffe's chapter reviews well this component of the ontoneurological examination.

There are, however, major problems with much of this publication in that there is no coherent theme running through it. Indeed, each chapter seems to have little connection with adjacent ones. It seems that each contributor was given a chapter to write and the editor merely stuck them together without rewriting or cross-referencing them. The net result is a painful variability in style, standard and usefulness. This is a pity as there are some nuggets of value here. As a result, as far as the neurologist is concerned this book is disappointing and unbalanced. For example, he will find a long discussion of aural symptomatology including a bizzare Latin binomial nomenclature more suited to a horticultural catalogue (p. 222) and only half a page on auditory evoked brainstem potentials, and he will certainly be surprised that a common cause for unilateral loss of semicircular canal function is acoustic neuroma (p. 103).

Unfortunately, this book cannot be recommended for the two or three good chapters it contains.

PETER RUDGE

The Acoustic Reflex: Basic Principles and Clinical Applications. Edited by Shlomo Silman. 1984. Pp. 528. Orlando, Florida: Academic Press. Price £46.00, $65.60.

In the last forty years, there has been considerable interest in the value of the acoustic reflex as a diagnostic tool in auditory pathology, but it is only in the last decade, with the advent of the electroacoustic-impedance bridge, that the technique has become widely available in clinical practice. The value of measurement of acoustic reflex function lies in the wealth of objective data appertaining to the middle ear, the eighth nerve and the brainstem, which may be obtained rapidly, using simple techniques. A comprehensive text on this subject is therefore long overdue.

This book is comprised of 14 chapters and emphasis has been placed on a multidisciplinary approach, such that many aspects of the acoustic reflex are covered, including anatomy, neurophysiology, physical and technical measurement, audiology, neurology and otolaryngology. Unlike many multiauthor publications, this book is remarkable, throughout, for the high standard of the individual contributions. Strict editorial control has produced a uniform format to each chapter with a historical review, an account of the current state of the art of each aspect and informed discussion of current controversies and theories. Considerable emphasis is placed on directives for future work and every chapter, without exception, is appended by an excellent reference list.

Although this book is an outstanding reference volume on the acoustic reflex and invaluable to any scientist or clinician interested in the auditory system, it will be of limited interest to the neurologist or neurosurgeon with the exception of Møller's chapter on the neurophysiology of the acoustic reflex and a short chapter on the effect of drugs and systemic disease on the reflex. In this latter chapter, multiple sclerosis and myasthenia gravis are discussed in some detail, but the author, Mangham, emphasizes the need for further work in this area and highlights the paucity of literature available on the acoustic reflex in neurological disorders.

L. M. LUXON

Current Topics in Membranes and Transport. Volume 22. **The Squid Axon.** Edited by Peter F. Baker. 1984. Pp. 593. Orlando, Florida: Academic Press. Price £62.50, $ 69.00.

From its discovery by Williams at the turn of the century and the highlighting of its significance by J. Z. Young in 1939, the giant fibre system of the cephalopodia has held a preeminent position in neuroscience as an ideal preparation for a wide variety of fundamental studies employing electrophysiological, biochemical and pharmacological approaches. This book, which represents another fine contribution to the series of volumes published under the title *Current Topics in Membranes and Transport*, fully justifies Young's prediction through a constellation of critical reviews that summarize the advances that have stemmed from the study of giant axons. The editor can be congratulated on his choice of contributors and for encouraging them to include introductory didactic accounts summarizing key concepts, which are of particular value to the less specialist reader seeking general enlightenment in these complex subjects, as well as to provide up-to-date information, the most recent references being dated 1982.

The book comprises four parts designated Structure, Regulation of Axoplasmic Environment, Excitability, and Interactions between Giant Axons and Neighbouring Cells. These encompass 19 chapters whose topics range from axoplasmic structure, sugar and amino acid transport, the sodium pump, membrane surface charge, noise analysis and channel properties and the pharmacological analysis of Na channels, to the study of synaptic transmission at the giant squid synapse, each being authoratatively written by experts in their field.

Although attention is entirely focused on the squid axon, the fundamentals emerging from its study are so far reaching that the book should find wide appeal among neuroscientists interested in mechanisms at the cellular; membrane and molecular level, although the price may well limit its purchase to libraries. Be this as it may this volume stands as a *Festschrift* for a noble animal whose giant axon, encouraged, among others, by an occasional firm squeeze from the editor P. F. Baker, has rewarded mankind by a great deal of intellectual activity, interest and enjoyment.

T. A. Sears

Psychopharmacology of the Limbic System. British Association for Psychopharmacology, Monograph 5. 1984. Pp. 266. Oxford University Press. Price £17.50.

Coexistence of Neuroactive Substances in Neurons. Edited by Victoria Chan-Palay and Sanford L. Palay. 1984. Pp. 433. New York and Chichester: John Wiley. Price £85.45.

Neurology and Biology, Volumes 8A, B and C. **Catecholamines.** Part A. **Basic and Peripheral Mechanisms.** Pp. 420. B. **Neuropharmacology and CNS Theoretical Aspects.** Pp. 520. C. **Neuropharmacology and CNS Therapeutic Aspects.** Pp. 260. Edited by Earl Usdin, Arvid Carlsson, Annica Dahlström and Jorgen Engel. 1984. New York: Alan Liss. Prices A, £91.00; B, £107.00; C, £72.00.

All three volumes arise from the proceedings of scientific meetings, and suffer from the weaknesses inherent in such publications of inconsistencies of style, patchiness of content and lack of strong editorial control. The genre continues to have a seductive fascination for researchers, however, because these shortcomings are compensated for by the topicality of content in these volumes. What other way, apart from dealing with the avalanche of primary scientific pubications, do we have of keeping up to date in our field?

The three publications, although they all concern chemical messengers and neuropharmacology, address quite different subjects. *Psychopharmacology of the Limbic System* looks at an old subject from a new perspective. Since the description of the limbic system by Paul Broca more than a century ago there has been intense interest in the anatomy and physiology of these neural pathways which represent the neurological basis of emotional behaviour. There has been growing recognition also that the limbic system represents a key target for many psychoactive drugs, and this volume reviews the evidence for this notion. The 17 chapters are the proceedings of a meeting of the British Association for Psychopharmacology held in 1983. They give a good up-to-date survey of modern knowledge of the anatomy, chemistry and neurophysiology of the limbic system, and its relation to emotional behaviour. Considerable focus is given to the limbic system in relation to epilepsy, including reviews of amygdaloid kindling, temporal lobe epilepsy and the actions of anticonvulsant drugs. Another key area concerns the limbic system as a target for the antischizophrenic actions of neuroleptic drugs, and the possible neurochemical and neuropeptide abnormalities that may exist in schizophrenia. The actions of benzodiazepines and antidepressants on the limbic system are also discussed. This small volume serves a useful function in providing a concise survey of a complex and topical area of psychopharmacology research.

Coexistence of Neuroactive Substances in Neurons, based on a symposium held in 1982 at the National Institutes of Health, also gives a valuable review of an entirely new area of neurochemistry/neuropharmacology research. This stems from the recognition that neurons may contain more than one neuroactive substance, with neuropeptides coexisting with each other or with conventional monoamine or amino acid neurotransmitters. These observations depend very largely on recent advances in immunostaining technology, which permit staining of more than one antigen on the same tissue sections. Unambiguous evidence for coexistence at the single cell level can thus be obtained. The 25 chapters in this volume give the first comprehensive review of this topical area of research. Old concepts of the chemical labelling of the nervous system have been upset by these modern findings. Thus we now know that adrenergic and cholinergic neurons of the peripheral autonomic nervous system may contain peptides (e.g. enkephalins, somatostatin, vasoactive intestinal polypeptide, neuropeptide Y) in addition to the traditional noradrenaline or acetylcholine. Numerous examples of coexistence can be found in the CNS, often again upsetting conventional thinking. In the cerebellum, for example, the Purkinje cells have long been considered as a homogeneous population of GABAergic neurons, but the new staining methods reveal that the GABA synthetic enzyme, glutamate decarboxylase, is not present uniformly in all Purkinje cells; some contain a peptide (motilin) and there is a third possible transmitter candidate, taurine, whose presence can be inferred by the occurrence of the synthetic enzyme cysteine sulphinic acid decarboxylase in some Purkinje cells. In the raphe nucleus of brainstem, the cells previously considered as a simple population of serotonin neurons are now seen to be a complex mixture—some containing only serotonin, some a mixture of serotonin with TRH or with substance P or GABA. Many other examples are described, perhaps the most complex neurons being those of the magnocellular neurosecretory nuclei in the hypothalamus, which may contain many other substances (enkephalins, dynorphins, cholecystokinin, somatostatin, acetylcholine, noradrenaline) in addition to oxytocin or vasopressin.

The functional significance of coexistence remains unclear, although some examples of synergism between cosecreted substances have been described. What is clear is that the phenomenon of coexistence of neuroactive substances in neurons greatly enlarges our understanding of the complexity of chemical signalling in the nervous system. Whereas previously we had thought of perhaps a dozen neurotransmitter chemicals with the more recent addition of another 30 or more neuropeptides, we now have to consider that many hundreds or even thousands of different chemical signals can be employed in neural signalling, given the possibility of two- or three-way permutations of coexisting substances. The concept of the neuron having a fixed phenotypic expression of neurotransmitter/neuropeptide content throughout its life time is also no longer valid; in tissue culture or during normal development this phenotype can be radically altered (from cholinergic to adrenergic, or *vice versa*, for example). This is a valuable review volume, made less so only by the fact that two years have elapsed since the original meeting, and by the absence of any contribution from Dr T. Hōkfelt or his colleagues, who have made such important contributions to the discovery and description of these new phenomena.

Catecholamines, Volumes A, B and C belongs to a different category of size and cost (at £270 for the three volume set, containing some 150 short chapters, surely one of the most expensive symposium volumes ever). It represents the proceedings of the 5th International Catecholamine Symposium, held in Göteborg in June 1983. The volumes attempt the almost impossible task of reviewing all aspects of modern catecholamine research, from basic neurochemical studies, to neuropharmacology, to clinical applications. While there is much of value here, the format of numerous short chapters with considerable overlap of content does not make for easy reading. One is tempted to speculate that while catecholamine research probably represents an area of gradually waning scientific interest, the symposia and resulting publications continue to get bigger, and may eventually—like the dinosaur—outgrow their usefulness. This certainly could not be recommended as a good buy except as a reference work for libraries.

LESLIE L. IVERSEN

Ganglioside Structure, Function and Biomedical Potential. Advances in Experimental Medicine and Biology, Volume 174. Edited by Robert W. Ledeen, Robert K. Yu, Maurice M. Rapport and Kunihiko Suzuki. 1984. Pp. 649. New York: Plenum Press. Price $89.50.

About fifty years ago Klenk's analysis of Tay-Sachs brain tissue led to the discovery of the gangliosides. It now emerges that these amphipathic glycolipids constitute a family of some 100 different molecular species composed of a ceramide moiety with varying proportions of oligosaccharide chains and sialic acid residues. Although distribution is not exclusive to nervous tissue the lipid is concentrated in grey matter. Speculation that gangliosides have a functional role within nerve cells quickly attracted attention. Thus a symposium on the subject was held in Vancouver in July 1983 and this is the basis of the present volume.

The first half of the book contains 24 contributions on chemistry, distribution, transport, metabolism, mutants and development. The articles are generally well written and up to date, complementing older reviews on the subject (e.g. Volume 125, 1980, in the same series). The remainder of the book deals with more biological and medical aspects of the topic. An example is the role of gangliosides as receptors for bioactive factors (toxins, viruses, hormones, etc.) and the suggestion that they may modulate coupling of neurotransmitters to adenylate cyclase.

There is a great deal of current interest in the part played by gangliosides in neurological disease not only in certain rare metabolic disorders but also in some conditions in which ganglioside abnormalities occur secondarily. The glycolipids themselves may have a pathological role, possibly in multiple sclerosis and in the induction of experimental autoimmune encephalomyelitis. There is also the more controversial possibility of gangliosides acting as therapeutic agents. Following brain lesioning, exogenous gangliosides are capable of enhancing sprouting and survival of nerve cells and functional recovery can be demonstrated. This most interesting research has prompted trials of gangliosides in neuropathies and in degenerative conditions such as motor neuron disease, but so far the clinical responses do not reflect the exciting promise shown by experimental research.

The value of this large book lies in its reports of contemporary work from a number of different disciplines. Those neuroscientists interested in the development of factors stimulating neural regeneration will find it particularly useful.

A. N. DAVISON

√**Oligodendroglia. Advances in Neurochemistry,** Volume 5. Edited by William T. Norton. 1984. Pp. 351. New York: Plenum Press. Price $49.00.

Oligodendroglia are one of the three main cell types of the central nervous system accounting for more than a quarter of the dry weight of the adult brain. Their main function is the synthesis and maintenance of the myelin sheath. In the first chapter in this fifth volume of *Advances in*

Neurochemistry, the morphological, developmental and more general properties of the oligodendrocyte are reviewed. There is an interesting account of the development of morphological research including reference to the transformation of a multipotential glioblast into the mature glial cell. In other parts of the book brief mention is made concerning the use of monoclonal antibodies which have been applied so successfully to the concept of the progenitor glial cell. Indeed it is evident that finding specific antigenic determinants for identification of oligodendrocytes remains a major objective in neurobiology. One possibility is myelin basic protein but this polypeptide is only seen briefly during myelinogenesis and in the mature cell the concentration of the surface antigen appears to be undetectable. Cerebroside and some enzymes may prove more practicable 'markers' for the oligodendroglial cell. An example is carbonic anhydrase which is widely distributed in both cytoplasmic and membrane-bound locations. There are then two chapters on the *in vivo* metabolism of glial lipid and protein. Possible mechanisms for the insertion of membrane components into the maturing sheath are given and the question of metabolic stability of myelin is reviewed. Recent work indicates that myelin phospholipid and basic protein undergo turnover whereas other components are more stable. Many of the ingenious methods devised for studying myelin metabolism should be applicable to research on pathological changes (e.g. demyelination) and the mechanisms of myelin synthesis and remyelination. The use of tissue culture for maintaining mature and developing oligodendroglia is reviewed by several contributors. Tissue culture is a convenient technique for basic studies such as on lipid metabolism or for research on trophic factors. The method is also valuable for studying genetic (jimpy, reeler mice, etc.) and pathological factors. It seems that culture of human glial cells remains a difficult problem for further research. The last chapter is devoted to regulation and differentiation of glia with an emphasis on the expression of proteins, particularly enzymes. The molecular mechanisms involved focus attention on the importance of these gene products to the state and physiological functioning of oligodendrocytes.

This book can therefore be recommended to neuroscientists as an excellent well-produced and generally up-to-date survey of the neurochemistry of the oligodendrocyte.

A. N. DAVISON

Central and Peripheral Endorphins: Basic and Clinical Aspects. Edited by E. E. Müller and A. R. Genazzani. 1984. Pp. 340. New York: Raven Press. Price $68.50.

This volume is a compilation of papers delivered in 1983 at a meeting on Recent Progress in Opioid Research organized by the Italian Society of Endocrinology. Raven Press should be congratulated on the rapidity in the publication of this volume, but should perhaps reconsider their policy of automatic publication of such meetings.

This book is a good example of what happens when there is no editorial control over the publication of a mass of papers presented at a large meeting. The meeting itself was doubtless very stimulating for the participants and I would suspect that most of the value came from informal discussions within the meeting. The publication, however, of a series of short papers, many only four pages long, of a standard from excellent to frankly very poor, offers very little to the prospective purchaser. Much better and more complete review articles are readily available in the literature, or from well constructed symposia, whilst in such a rapidly moving area of research only current peer reviewed journals will keep you up to date with the most recent advances.

There are of course several articles which are informative and well written, and it is possible to mention some from among the 45 chapters in the book. Tomas Hökfelt's description of the distribution of dynorphin peptides, C. H. Li's clear exposition of beta-endorphin structure-action relationships, Chrétien's description of regional differences in acetylation of POMC peptides and Herz's description of endogenous ligands of the different opioid receptors, were clear short reviews in areas of great interest. In the physiology section, Costa's decription of interactions between enkephalins and other transmitters, Tilder's work on opioid release from the hypothalamus, and Holaday and Tortella's paper on opioid functions *in vivo*, were all of interest—but even here the brevity of the articles does not allow proper assessment of the areas studied.

I am afraid this volume only has a role as a record of the meeting. It cannot be recommended either to a specialist in the area who will need the current literature, or to a browser who will get only a poorly balanced and confused view of this very important area of research.

STAFFORD LIGHTMAN

FORTHCOMING EVENTS AND ANNOUNCEMENTS

Fourteenth International Summer School of Brain Research on Ageing of the Brain and Senile Dementia

This will be held on August 26–30, 1985, in Amsterdam, The Netherlands. The intention of the Summer School is to present high level didactic reviews of important topics on ageing of the brain and senile dementia to an audience of young researchers working in different branches of the neurosciences Topics to be discussed will include neurophysiological, neuropathological and neurochemical changes with ageing and in senile dementia; animal models and aetiological factors relevant for ageing and senile dementia; new developments in therapeutic strategies.

For further information please contact Mrs W. Chen-Pelt, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam ZO, The Netherlands

The Joint Committee on Education.
American Association of Neurological Surgeons
and
Congress of Neurological Surgeons

Under the auspices of the Research Subcommittee of the Joint Committee on Education of the AANS and CNS, a registry of clinical trials in neurosurgery is being established. The purpose of this registry is to make available to all neurosurgical investigators basic information on clinical trials of neurosurgical interest that are being designed or conducted, so that investigators planning such a study can avoid duplicating work already in progress or completed and be put in contact with other investigators with similar interests who might wish to become involved in collaborative work.

For further information about the registry please contact Stephen J. Haines, MD, Department of Neurosurgery, University of Minnesota, Box 96 Mayo, Minneapolis, MN 55455. Tel: (612) 373-8785.

Sixth General Meeting of the European Society for Neurochemistry

This will be held in Prague, Czechoslovakia, on September 1–6, 1986. The programme will consist of symposia, workshops, round-table discussions, posters and plenary lectures devoted to all areas of the normal and pathological biochemistry of the nervous system, including neuropharmacological aspects. For further information, and forms for registration and abstracts, please contact Dr S. Tuček, Institute of Physiology, Academy of Sciences, Vídeňská 1083, CS-14220 Prague, Czechoslovakia.

Travel Grants For Young Neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
    - (a) an abbreviated curriculum vitae and a list of any relevant publications;
    - (b) statement of age and post currently held;
    - (c) a concise account of the purpose of the proposed visit;
    - (d) a recommendation from the head of department (where appropriate);
    - (e) a letter of acceptance from the department to be visited;
    - (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always to taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr. M. J. G. Harrison
Reta Lila Weston Institute of
Neurological Studies,
Middlesex Hospital Medical School,
London W1N 8AA

Reduced Subscription Rates

A reduced subscription rate (£20.00 per annum) is available to young subscribers under the age of 40 years, who are in a training post in clinical neurology or in the neurosciences in the UK. Applications for this special rate should be made to Dr. M. J. G. Harrison, The Middlesex Hospital, Mortimer Street, London, W1N 8AA with a letter from the head of department confirming the applicant's eligibility.

Printed in Great Britain
at the University Press, Oxford
by David Stanford
Printer to the University